COGNITIVE ENHANCEMENT IN PSYCHIATRIC DISORDERS

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COGNITIVE ENHANCEMENT IN PSYCHIATRIC DISORDERS

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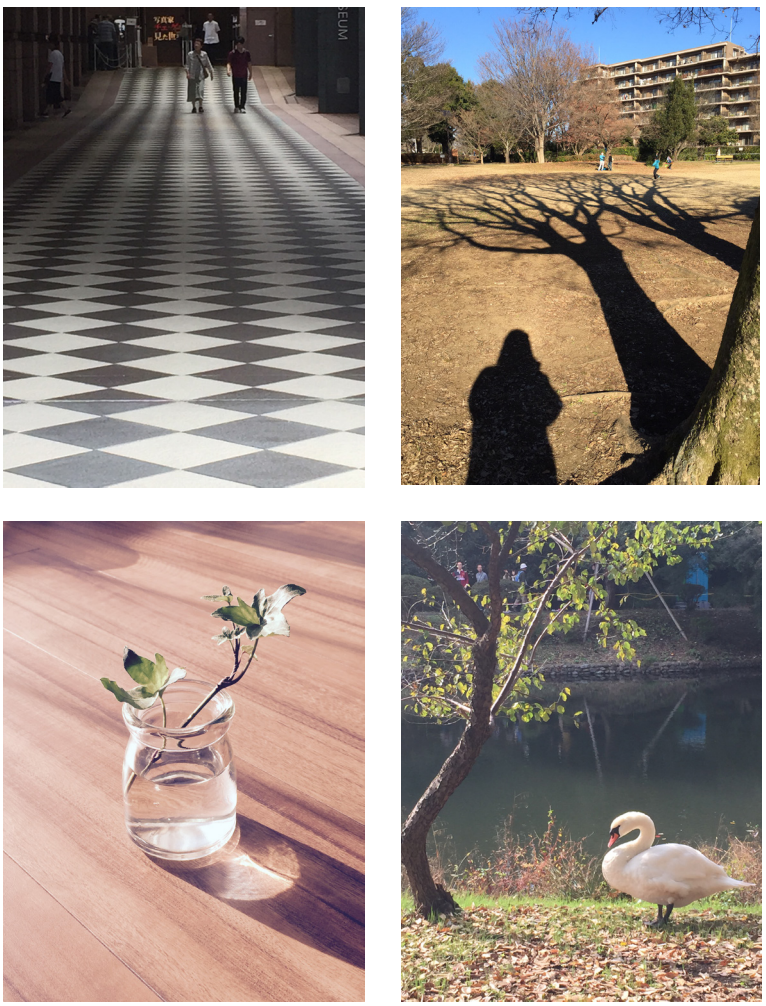

Image: Cognitive Health
"To overcome cognitive difficulties brings about peace of mind".
Scenes photographed by Tomiki Sumiyoshi

Disturbances of various domains of cognitive function have been shown to provide a major determinant of outcome for patients with psychiatric conditions. Cognitive impairment is present in an array of diseases, including schizophrenia (with its prodromal stage), mood disorder, autism spectrum disorder, obsessive-compulsive disorder, anxiety disorder, post-traumatic disorder, and eating disorder. In an effort to develop effective therapeutics for cognitive impairment, bridging of preclinical and clinical evidence has been attempted.

This edited Book will provide a forum for researchers and clinicians interested in the phenomenology, underlying mechanisms, and treatment of cognitive impairment associated with psychiatric illnesses. Twenty-eight contributions from 8 countries in Europe, Middle East, Asia, North America, and South America represent studies dealing with genetic, molecular, imaging, physiological, psychological, and behavioral issues. Information in this Book will facilitate the development of therapeutics of greater clinical value.

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EDITORIAL
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Editorial: Cognitive Enhancement in Psychiatric Disorders

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Editorial on the Research Topic

Cognitive Enhancement in Psychiatric Disorders

Disturbances of various domains of cognitive function, e.g., several types of memory, executive function, attention, fluency, and attention/information processing, have been shown to provide a major determinant of outcome for patients with psychiatric conditions. Cognitive impairment is present not only in people with dementias but also in an array of diseases, including schizophrenia (with its prodromal stage), mood disorders, autism spectrum disorders, and eating disorders. This is in line with the Research Domain Criteria (RDoC) initiative proposed by National Institute of Mental Health in the USA, designating the Cognitive System as one of the functional domains whose impairment is pertinent to various operational diagnoses. Intervention into cognitive impairment has been recognized as a major goal of clinical practice, but much remains to be explored.

Articles in this *Topic* deal with genetic, molecular, imaging, physiological, psychological, and behavioral issues regarding the mechanisms, assessment, and treatment of cognitive disturbances in psychiatric illnesses. Twelve *original researches*, nine *reviews*, five *mini-reviews*, one *protocol*, and one *opinion* have been contributed by authors from eight countries in Europe, Middle East, Asia, North America, and South America.

To attain the aims of initiatives, such as RDoC, it is essential to elucidate the biological bases for abnormalities of specific cognitive problems. The first paper, Genetic Biomarkers on Age-Related Cognitive Decline by Lin et al. concerns the search for genetic biomarkers of cognitive aging. A review was provided on studies of candidate genes and genome-wide associations, as well as gene–environment interactions paradigms, which is relevant to the prevention and development of novel therapeutics. Also, Pu et al. in Right Frontotemporal Cortex Mediates the Relationship between Cognitive Insight and Subjective Quality of Life in Patients with Schizophrenia present data on cortical activities in the brain, as evaluated by near-infrared spectroscopy. Another powerful tool to assess brain functions *in vivo* is positron emission tomography (PET). Thus, Takano summarizes the role for receptor subtypes and transporters for dopamine, serotonin, and norepinephrine, as evaluated by PET, in cognitive disturbances of schizophrenia (Cognitive Function and Monoamine Neurotransmission in Schizophrenia: Evidence From Positron Emission Tomography Studies).

Neurophysiological evaluation in relation to behavioral changes associated with cognitive function has been an area of intensive research. Accordingly, Sueyoshi and Sumiyoshi provide a brief overview on this issue with particular focus on electrophysiological markers, including electroencephalogram (Electrophysiological Evidence in Schizophrenia in Relation to Treatment Response). For mood disorders, the study by Matsuo et al. (Sensorimotor Gating in Depressed and Euthymic Patients with Bipolar Disorder: Analysis on Prepulse Inhibition of Acoustic Startle Response Stratified by Gender and State) presents data of prepulse inhibition (PPI) of

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the acoustic startle reflex. These authors found PPI disruption in patients with bipolar disorder only if they are male and depressed, suggesting that this behavioral phenotype is both trait- and state-specific. The same group of investigators also report that *weak* handgrip strength and *high* body mass index are disadvantageous for cognitive function in patients with schizophrenia (Relationship of Handgrip Strength and Body Mass Index With Cognitive Function in Patients With Schizophrenia by Hidese et al.), providing a potential *physical index* for cognitive performance. Much attention has been paid to early intervention into cognitive and social outcomes in psychosis. This topic was reviewed in Early Intervention and a Direction of Novel Therapeutics for the Improvement of Functional Outcomes in Schizophrenia: A Selective Review by Kurachi et al., who summarized evidence for morphological changes in the brains of individuals with schizophrenia, and provides perspectives of novel treatments.

The implementation of reliable and valid assessment methods of cognition, capable of predicting social function, is one of the most important research topics. Specifically, Sumiyoshi et al. investigated high-level cognitive functions, using a text-mining technique, in individuals with schizophrenia, as reported in Semantic Memory Organization in Japanese Patients With Schizophrenia Examined With Category Fluency (by Sumiyoshi et al.). Comparisons of high-level cognitive function between subtypes of schizophrenia were attempted by Tyburski et al. (Neuropsychological Profile of Specific Executive Dysfunctions in Patients With Deficit and Non-deficit Schizophrenia), who observed the ability of performance on specific cognitive domains to predict long-term outcomes. For this clinical issue, Ohi et al. used the difference between premorbid and current IQs as a surrogate index of cognitive function in patients with schizophrenia (A Brief Assessment of Intelligence Decline in Schizophrenia as Represented by the Difference Between Current and Premorbid Intellectual Quotient).

Compared with schizophrenia, the degree of cognitive decline is milder in mood disorders, suggesting the need for using neuropsychological tests with greater sensitivity. Accordingly, Sumiyoshi et al. report the utility of the California Verbal Learning Test, with greater cognitive demands compared with other word list learning tests typically used for schizophrenia, in evaluating memory disturbances in patients with euthymic bipolar disorder (Verbal Memory Impairment in Patients with Subsyndromal Bipolar Disorder). Cognitive function also plays an important role in decision-making capacity of patients in the event of consenting to participate in clinical studies, receiving medical treatments, and so on. This critical issue is discussed by Sugawara et al. in Competence to Consent and Its Relationship With Cognitive Function in Patients With Schizophrenia. Overall, future research will be benefitted by incorporating objective markers to facilitate the understanding of the link between cognitive performance and real-world functional outcomes.

In an effort to develop effective therapeutics for cognitive impairment, translational approaches, i.e., bridging preclinical and clinical evidence, have been attempted. However, clinical trials of agents, produced through such approaches, have yielded negative results in most cases, indicating a need for further study. This challenge was summarized by Hsu et al. who provided a review of the literature on the efficacy of several drugs, i.e., putative "cognition enhancers" based on preclinical data, in treating cognitive impairment of psychiatric and neurological diseases (Medications Used for Cognitive Enhancement in Patients With Schizophrenia, Bipolar Disorder, Alzheimer's Disease, and Parkinson's Disease). The paucity of effective compounds to date is related to the initiative of the switch to other administration routes for the same drug, as reported by Hori et al. in Effects of Continuing Oral Risperidone vs. Switching from Risperidone to Risperidone Long-Acting Injection on Cognitive Function in Stable Schizophrenia Patients: A Pilot Study.

To overcome this situation, research into some of the novel agents is addressed. Thus, Guercio and Panizzutti provide a review of studies on the possible cognition-enhancing effect of D-serine, a co-agonist at N-methyl-D-aspartate receptors, and related compounds (Potential and Challenges for the Clinical Use of d-Serine as a Cognitive Enhancer). On the basis of animal data on spatial memory, Svoboda et al. discussed the role for subtypes of muscarinic acetylcholine receptors as a potential target for drug development (Drugs Interfering with Muscarinic Acetylcholine Receptors and Their Effects on Place Navigation). In addition to these agents, neurotrophic compounds, anti-inflammatory/oxidation agents, and particular nutrients may provide a novel candidate for pharmaco-therapeutics in this field. Also, whether prolonged administration of antipsychotic drugs is advantageous for improving cognition social function in schizophrenia and early psychoses has attracted attention. Accordingly, Omachi and Sumiyoshi examined results from relevant studies on this issue in Dose Reduction/Discontinuation of Antipsychotic Drugs in Psychosis; Effect on Cognition and Functional Outcomes, which should provide a clue to improving long-term consequences of quality of life for patients.

There is also a growing trend to develop non-pharmacologic therapeutics for ameliorating cognitive deficits in psychiatric illnesses. In particular, promising results have been reported for several types of cognitive remediation, or rehabilitation in schizophrenia and other diseases. Mogami contributed an *Opinion* on the Neuropsychological Educational Approach to Remediation (NEAR), one of the landmark methods of cognitive training (Cognitive Remediation for Schizophrenia with Focus on NEAR). Efficacy of this type of cognitive rehabilitation has been reported mainly for relatively young people with schizophrenia. With a well-controlled study design, Choi et al. found that disturbances of some of the key cognitive domains were alleviated also in older patients with chronic schizophrenia (Cognitive Remediation in Middle-Aged or Older Inpatients With Chronic Schizophrenia: A Randomized Controlled Trial in Korea). Several factors have been suggested to intervene the effect of cognitive remediation in schizophrenia. For example, Takeda et al. provided a review of the role for intrinsic motivation in optimizing the benefits of cognitive training, with reference to neurobiological substrates measured by brain imaging methods (Neural Correlates for Intrinsic Motivational Deficits of Schizophrenia; Implications for Therapeutics of Cognitive Impairment).

Recent efforts have been directed to boost the effect of cognitive rehabilitation with biological strategies, such as medications and non-invasive brain stimulation (neuromodulation). In this line, Harvey and Sand examined the current state of interventions combining cognitive and psychosocial treatments with pharmacological agents, such as stimulants, plasticity-inducing compounds, or attentional enhancers (Pharmacological Augmentation of Psychosocial and Remediation Training Efforts in Schizophrenia). For non-pharmacological approach, Jahshan et al. presented an update on co-treatment with physical exercise or transcranial direct current stimulation (tDCS), a type of neuromodulation (Enhancing Neuroplasticity to Augment Cognitive Remediation in Schizophrenia). Physical exercise is thought to stimulate neuroplasticity through the regulation of central growth factors, while the mechanisms of tDCS may involve long-term potentiation.

tDCS is the subject for a series of articles in this *Research Topic*, in accord with emerging evidence for the efficacy of neuromodulation in improving cognitive function. Thus, Narita et al. observed stimulation of the left prefrontal cortex with tDCS improved some domains of cognition, e.g., verbal memory, in patients with schizophrenia (Possible Facilitative Effects of Repeated Anodal Transcranial Direct Current Stimulation on Functional Outcome 1 Month Later in Schizophrenia: An Open Trial). Importantly, daily-living skills or "functional capacity" was also enhanced, providing the first report on the ability of tDCS to improve the higher-level functional outcome. These findings were based on an open-label trial, and the same group of investigators are conducting a confirmatory study with a more rigorous design (Effect of Transcranial Direct Current Stimulation on Functional Capacity in Schizophrenia: A Study Protocol for a Randomized Controlled Trial by Narita et al.). Several types of neuromodulation, such as tDCS, transcranial alternating current stimulation, and transcranial magnetic stimulation are also expected to enrich the treatment options for cognitive impairment in Alzheimer's disease, as summarized by Chang et al. (Brain Stimulation in Alzheimer's Disease).

Cognitive function and its dysregulation have been a topic of research on psychiatric conditions common in children and adolescents. Among the behavioral phenotypes typical of developmental disorders, sensory symptoms are included in the diagnostic criteria for autism. With a focus on acoustic startle response, Takahashi et al. observed that exaggerated acoustic reactivity was associated with skewness of locomotor activity in boys with autism spectrum disorders (Acoustic Hyper-Reactivity and Negatively Skewed Locomotor Activity in Children With Autism Spectrum Disorders: An Exploratory Study). In young women with attention-deficit/hyperactivity disorder (ADHD), gains of procedural memory consolidation were greater with the evening rather than morning training, unlike the case for individuals with typical development, as reported by Korman et al. (Procedural Memory Consolidation in Attention-Deficit/Hyperactivity Disorder Is Promoted by Scheduling of Practice to Evening Hours).

Impaired cognitive function has also been suggested to underline some aspects of the psychopathology of eating disorders. Thus, Tamiya et al. compared cognitive profiles between the restricting type and binge-eating/purging type of anorexia nervosa, and found significantly worse attention/vigilance for the latter type, which may be related to the higher mortality rate (Neurocognitive Impairments Are More Severe in the Binge-Eating/Purging Anorexia Nervosa Subtype Than in the Restricting Subtype).

These days, we occasionally receive a message "Tomiki (Kenji), an article you edited reached an impact milestone." At the time of completion of this *Editorial*, the number of "views" of our *Topic* has reached almost 73,000, thanks greatly to the dedicated authors worldwide. This status assures us that our endeavor to "make a forum for researchers and clinicians interested in cognitive impairment of psychiatric illnesses" has been attained. This collaborative work accomplished by our colleagues will help facilitate the development of therapeutics of greater clinical value.

AUTHOR CONTRIBUTIONS

TS wrote the first draft of the manuscript, and KH provided opinions on it. Both authors read and approved the submitted version.

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REVIEW
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Genetic Biomarkers on Age-Related Cognitive Decline

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With ever-increasing elder populations, age-related cognitive decline, which is characterized as a gradual decline in cognitive capacity in the aging process, has turned out to be a mammoth public health concern. Since genetic information has become increasingly important to explore the biological mechanisms of cognitive decline, the search for genetic biomarkers of cognitive aging has received much attention. There is growing evidence that single-nucleotide polymorphisms (SNPs) within the *ADAMTS9*, *BDNF*, *CASS4*, *COMT*, *CR1, DNMT3A*, *DTNBP1, REST*, *SRR*, *TOMM40*, circadian clock, and Alzheimer's diseases-associated genes may contribute to susceptibility to cognitive aging. In this review, we first illustrated evidence of the genetic contribution to disease susceptibility to age-related cognitive decline in recent studies ranging from approaches of candidate genes to genome-wide association studies. We then surveyed a variety of association studies regarding age-related cognitive decline with consideration of gene–gene and gene–environment interactions. Finally, we highlighted their limitations and future directions. In light of advances in precision medicine and multi-omics technologies, future research in genomic medicine promises to lead to innovative ideas that are relevant to disease prevention and novel drugs for cognitive aging.

Keywords: Alzheimer's diseases, biomarker, age-related cognitive decline, cognitive aging, gene–gene interactions, neurodegeneration, single-nucleotide polymorphisms, SNP–SNP interactions

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INTRODUCTION

Generally speaking, age-related cognitive decline, or cognitive aging, is recognized as a gradual and enduring process of transition in cognitive capacity with increasing age (1). Although cognitive decline is common in old age, the relationship between aging and neurodegenerative disease such as dementia remains unclear. Whereas aging is a well-known risk factor for dementia, dementia is not an inevitable consequence of the process of aging. The concept and underlying mechanisms of normal aging and pathological aging might be different. It should be noted that cognitive aging may raise the likelihood of many age-associated diseases and neurodegenerative disorders, such as mild cognitive impairment (MCI), Alzheimer's diseases (AD), Parkinson's disease, and other dementias, due to the fact that prior research work has projected that rates of age-associated diseases and neurodegenerative disorders gain rapidly with advancing age (2). While ever-increasing elder populations exist in both developed and developing countries, the pervasiveness of age-associated

diseases and neurodegenerative disorders has become a huge public health concern owing to high social and economic burdens (3). What is more, cognitive aging processes implicate multiple complex pathogeneses including genetic and environmental factors (4). In this light, the identification of genetic biomarkers has become an important area of research that aims to preclude the advancement of cognitive aging and to grasp the biology of cognitive aging in an increasingly aging society (5). It is noteworthy that untangling genetic biomarkers for cognitive aging has been at the center of major investigations in the field of precision medicine, and the relevant biomarkers for AD are generally utilized in cognitive aging research as well because of the increased risk for AD in the elderly individuals (6).

More recent research in genome-wide association studies (GWAS) has implicated that single-nucleotide polymorphisms (SNPs) among 11 genes appear to affect the risk of AD, encompassing the *PICALM*, *MS4A6E*, *MS4A4E*, *MS4A4A*, *EPHA1*, *CR1*, *CLU*, *CD33*, *CD2AP*, *BIN1*, *APOE*, and *ABCA7* gene (7–11). Consequently, a meta-analysis of GWAS studies ($n = 74{,}046$) identified 14 risk genes in AD, encompassing the *ZCWPW1*, *SORL1*, *SLC24A4*, *RIN3*, *PTK2B*, *NME8*, *MEF2C*, *INPP5D*, *HLA-DRB4*, *HLA-DRB1*, *FERMT2*, *DSG2*, *CELF1*, and *CASS4* genes (12). The succeeding whole-exome sequencing analysis further tracked down the *PLD3* gene to likely be a risk gene for AD (13). Moreover, it has been found that cognitive decline was linked with the *CR1* rs6656401 SNP by using the established AD-associated genes (14). Additionally, recent epistasis studies suggested that the *CLU-MS4A4E* (15, 16) and *CD33-MS4A4E* (16) gene–gene interactions might have a considerable influence on the susceptibility of AD. By utilizing the known AD-associated genes, it has also been demonstrated that cognitive decline was related with the *ABCA7* rs3764650 and *CD33* rs3865444 SNPs in the elderly Caucasian women (17).

In this review, we first surveyed some genetic biomarkers that were linked with age-related cognitive decline in several recent association studies (**Table 1**). Furthermore, we assessed some potential gene–gene and gene–environment interactions on age-related cognitive decline. This review does not intend to comprehensively survey all literature. We mainly focused on the most recent developments for biomarker research in cognitive aging. Finally, the limitations and future perspectives associated with cognitive aging in terms of genetic biomarkers were summarized. Future replication studies in larger samples with longitudinal follow-up are required to confirm the findings of the biomarkers for cognitive aging discovered in the association studies.

RECENT ASSOCIATION STUDIES

AD-Associated Genes

As mentioned previously in the Section "Introduction," it has been revealed that AD risk is linked with *ZCWPW1*, *SORL1*, *SLC24A4*, *RIN3*, *PTK2B*, *PLD3*, *PICALM*, *NME8*, *MS4A6E*, *MS4A4E*, *MS4A4A*, *MEF2C*, *INPP5D*, *HLA-DRB4*, *HLA-DRB1*, *FERMT2*, *EPHA1*, *DSG2*, *CR1*, *CLU*, *CELF1*, *CD33*, *CD2AP*, *CASS4*, *BIN1*, *APOE*, and *ABCA7 in* GWAS and meta-analyses (7–12). To recognize probable genes implicated in the regulation of age-related cognitive decline, a recent association study has analyzed whether SNPs within these 27 AD-associated genes are linked with cognitive aging as well as via complex gene–gene and gene–environment interactions in a cohort of older Taiwanese adults ($n = 634$) aged over 60 years (mean age: 64.2 years) from the Taiwan Biobank (18). In order to weigh cognitive functions, the mini-mental state examination (MMSE) method was administered for all participants (18). Lin et al. tested 588 SNPs, but only the *CASS4*-rs911159 SNP persisted significant for cognitive aging

TABLE 1 | Relevant studies in genetic biomarkers on age-related cognitive decline.

Gene	Study	Ethnic group	Results
ADAMTS9	Lin et al. (56)	Taiwanese (mean age: 64.2)	*ADAMTS9* (including rs9831846, rs4317088, rs9985304, and rs73832338) were linked with cognitive aging
APOE	De Jager et al. (30)	Various populations (mean age: 72.0~80.8)	*APOE* was genome-wide significantly correlated with cognitive aging for normal aging
BDNF	Laing et al. (34)	German (mean age: 72.7)	*BDNF* altered cognitive aging in healthy subjects for normal aging
CASS4	Lin et al. (18)	Taiwanese (mean age: 64.2)	*CASS4* rs911159 persisted significant for cognitive aging after Bonferroni correction for normal aging
COMT	Liu et al. (36); Papenberg et al. (37)	Taiwanese (mean age: 78.7) German (mean age: 64.9~65.3)	*COMT* Val158Met contributed to individual differences in cognitive aging
CR1	Chibnik et al. (14)	non-Hispanic white (mean age: 75.5~84.4)	*CR1* was significantly associated with cognitive aging for normal and pathologic aging
DNMT3A	Chouliaras (78)	Dutch (mean age: NA)	*DNMT3A* rs11887120 was associated with cognitive decline for normal aging
REST	Lin et al. (67)	Taiwanese (mean age: 64.2)	*REST* rs1277306 was linked with cognitive aging for normal aging
TOMM40	Davies et al. (86)	Various populations (mean age: 64.6~79.1)	*TOMM40* rs2075650 was significantly associated with cognitive aging for normal aging
Circadian clock genes	Lin et al. (42)	Taiwanese (mean age: 64.2)	*RORA* rs13329238, *NPAS2* rs17655330, *CLOCK* rs3749473, and *RORB* rs10781247 individually and interactively altered cognitive aging for normal aging

after Bonferroni correction (18). In addition, their analysis results suggested an association with 6 more SNPs in the AD-related genes, encompassing the *SLC24A4*-rs67063100, *RIN3*-rs1885747, *PLD3*-rs11672825, *MEF2C*-rs9293506, *FERMT2*-rs4901317, and *EPHA1*-rs10952552 SNPs (18). Lin et al. also displayed the gene–gene interactions among the *SLC24A4*-rs67063100, *MEF2C*-rs9293506, *FERMT2*-rs4901317, *EPHA*-rs10952552, and *CASS4*-rs911159 SNPs on cognitive aging by using the generalized multifactor dimensionality reduction (GMDR) approach (18). Furthermore, they disclosed the gene–environment interactions of the *MEF2C*-rs9293506 and *SLC24A4*-rs67063100 SNP with environmental factors including social support, physical activity, smoking status, and alcohol consumption on cognitive aging by using the GMDR approach (18).

Consistent with the findings by Lin et al. (18), two preceding GWAS studies (8, 10) have reported that the *EPHA1* rs11767557 SNP may affect the vulnerability to AD. In addition, the *FERMT2* rs17125944, *MEF2C* rs190982, and *SLC24A4* rs10498633 SNPs were prone to AD in a meta-analysis study (12). Moreover, a whole-exome sequencing study pinpointed a rare rs145999145 (Val232Met) variant in the *PLD3* gene was liable to AD (13). The *PLD3* gene may play a central role in dealing with amyloid-beta precursor protein (13).

The CASS4 protein is proposed to better characterize the functions of cell growing, spreading, adhesion, and other activities (19). Moreover, it was speculated that *CASS4* plays a vital part in the hallmarks of AD such as the amyloid precursor protein (APP) and Tau protein (20). More recent studies also indicated an association between AD and the *CASS4* rs7274581, rs6024870, and rs16979934 SNPs (12, 21–23). In contrast, a replication study indicated that the *CASS4* rs7274581 SNP did not affect the risk of AD in a Spanish population (24).

Gene–gene interaction study inferred that *SLC24A4*, *MEF2C*, *FERMT2*, *EPHA1*, and *CASS4* synergistically raised the propensity of cognitive aging by using the GMDR approach (18). It was further speculated that these five genes are comprised in the relevant pathology and pathways (18). *EPHA1* is implicated in regulating neurodevelopment (20). *FERMT2* contributes to Tau neurotoxicity and cell adhesion (25). *MEF2C* may influence hippocampal synaptic connectivity and thereby mediate hippocampal-dependent memory and learning (26). *SLC24A4*, in the vicinity of the *RIN3* gene, is linked with neurodevelopment (27) as well as Tau pathology and APP (28).

APOE

The *APOE* gene, located on chromosome 19q13.32, encodes a major protein which is crucial for the regular catabolism of triglyceride-rich lipoprotein constituents (29). Conducting a GWAS study with the longitudinal cognitive testing data such as memory and perceptual speed, De Jager et al. discovered that *APOE* was genome-wide significantly correlated with age-related cognitive decline (mean age: 72.0~80.8 years) (30). A meta-analysis of 77 studies ($n = 40{,}942$) also suggested that carriers of the *APOE* ε4 allele, which were linked with late-onset AD, performed worse on several domains of cognitive functions including overall global cognitive ability, episodic memory, and executive functioning (31). Further, the *APOE* rs405509 and *APOE* rs440446 SNPs were more likely to develop non-pathological cognitive aging, independent of *APOE* major isoforms, in a Finnish population (32). In contrast, a replication study indicated that the *APOE* gene did not affect the risk of age-related cognitive decline in older Taiwanese adults (18).

BDNF

Another potential candidate gene such as *BDNF* was reported to be implicated in age-related cognitive decline among the elderly (33). The *BDNF* gene, encoding proteins of the nerve growth factor family, was demonstrated to alter cognitive deficits in healthy subjects (mean age: 72.7 years) for normal aging by using the mean Z-scores based on three cognitive domains including motor function, memory, and perceptual speed (34). Ward et al. also disclosed an interaction between *APOE* and *BDNF* that predicted a cognitive effect in healthy older adults (35).

COMT

The *COMT* gene, located on chromosome 22q11.21, is essential in the metabolic degradation of prefrontal dopamine (36). A functional *COMT* Val158Met polymorphism has been shown to contribute to individual differences in cognitive aging in Taiwanese (mean age: 78.7 years) and German (mean age: 64.9~65.3 years) populations using MMSE scores (36, 37). Based on a 4-year longitudinal study, Dixon et al. also revealed that the *APOE* and *COMT* genes are complementary biomarkers in normal cognitive aging and early MCI for older adults (38).

CR1

The *CR1* gene encodes a protein that plays a role in cellular binding and immune complexes (14). A replication study reported that the rs6656401 SNP in the *CR1* gene, which is one of the susceptibility loci for AD, was significantly associated with cognitive deficits (mean age: 75.5~84.4 years) for normal aging (in terms of global cognitive decline) as well as for pathological aging (in terms of global AD pathology) using the cognitive testing data such as memory and global cognition (14). A subsequent replication study also indicated that the rs4844609 SNP in the *CR1* gene modulates episodic memory decline and an interaction between *APOE* and *CR1* influences cognitive decline for normal aging and for pathological aging (39). In contrast, a replication study indicated that the *CR1* gene did not affect the risk of age-related cognitive decline in older Taiwanese adults (18).

Circadian Clock Genes

Circadian rhythms are instinctively recurring cycles that determine the timing of biological events such as energy metabolism, hormone release, and sleep–wake cycles (40). Additionally, dysregulation of circadian rhythms is characteristic of the natural process of ongoing aging and cognitive decline (40). The circadian rhythms are maintained and triggered by a composition of core circadian clock genes, which can be classified as vital genes on provoking circadian rhythms in specific cells (41).

Circadian clock genes, encompassing *RORB*, *RORA*, *PER3*, *PER2*, *PER1*, *NR1D1*, *NPAS2*, *CRY2*, *CRY1*, *CLOCK*, and *ARNT*, may be also involved in cognitive impairment (40, 41). To find out potential genes implicated in the regulation of age-related

cognitive decline, a recent study analyzed whether the 11 aforementioned core circadian clock genes as well as complex gene–gene and gene–environment interactions contributed to cognitive aging in more than 634 elderly individuals (mean age: 64.2 years) in Taiwan (42). As a result, four SNPs, including the *RORA*-rs13329238, *NPAS2*-rs17655330, *CLOCK*-rs3749473, and *RORB*-rs10781247 SNPs individually and interactively alters the hazard of cognitive deficits in terms of MMSE scores for normal aging (42). Finally, environmental factors such as smoking status, alcohol consumption, social support, and physical activity also interacted with these SNPs in regulating the liability of age-related cognitive decline (42).

CLOCK encodes a protein which creates the ARNTL/CLOCK heterodimeric protein with ARNTL (43). In addition, rs1554483, 3111, and rs4580704 *CLOCK* SNPs influenced the tendency to AD in Chinese subjects (44–46). However, these results were not confirmed in different populations (42).

The RORA and RORB proteins create a family of nuclear hormone receptors (47). These two genes were reported to have a key part in a wide variety of regulations; for instance, cellular metabolism, circadian rhythm, embryonic development, immunity, and inflammatory responses (48, 49).

It should be noted that *NPAS2* encodes transcription factors which are a component belonging to the basic helix-loop-helix family, and the ARNTL/NPAS2 and ARNTL/CLOCK heterodimeric proteins can bind to chromatin, bringing about the upregulation in gene expression for *PER1*, *PER2*, *PER3, CRY1*, and *CRY2* (50). In this manner, products of these *CRY1*, *CRY2*, *PER1*, *PER2*, and *PER3* genes build a complex that inhibits the action of the ARNTL-containing complexes and in turn forms a negative feedback loop (50).

Insulin Resistance-Associated Genes

To identify possible genes implicated in the process of age-related cognitive decline, a recent association study of the Taiwan Biobank has hypothesized that SNPs in insulin resistance-associated genes, including the *PPARG*, *GCKR*, and *ADAMTS9* genes, might be associated with cognitive aging individually or collectively in a cohort of Taiwanese individuals ($n = 547$; age > 60 years; mean age: 64.1 years) (51). The results indicated that 4 SNPs (including rs9831846, rs4317088, rs9985304, and rs73832338) within *ADAMTS9* were linked with MMSE scores (that is, cognitive aging) after performing Bonferroni correction (51). In addition, Lin et al. identified a SNP–SNP interaction between *ADAMTS9*-rs76346246 and *ADAMTS9*-rs9985304 that may influence cognitive aging by using the GMDR approach (51).

ADAMTS9 is demonstrated in the regulation of a wide variety of processes, such as the control of organ shape during growth, the inhibition of angiogenesis, and the cleavage of proteoglycans (51). Since one of the risk factors for cognitive aging and AD is insulin resistance, insulin resistance-related genes might be linked with cognitive aging (52, 53). Insulin abnormalities raise the uncertainty for neurodegenerative disorders including MCI, AD, and cognitive aging (54, 55). Insulin is also a fundamental factor for normal brain functioning. It should be noted that *ADAMTS9* is associated with insulin resistance, insulin sensitivity, and type 2 diabetes (56, 57). There is growing evidence that the ADAMTS-9 protein might participate in the processes of brain disease states including spinal cord injury, ischemic stroke, and transient middle cerebral artery occlusion in animal studies (58–60). In accordance, a GWAS study has identified the *ADAMTS9* rs6795735 SNP as a candidate biomarker for age-related macular degeneration, which commonly occurs in elder adults (61).

RE1-Silencing Transcription Factor (*REST*) Gene

A growing body of evidence suggests that *REST* may be involved with AD and cognitive aging (62). A recent replication study has assessed whether *REST* SNPs are associated with cognitive aging as well as via SNP–SNP interactions for normal aging in elder Taiwanese subjects ($n = 634$; mean age: 64.2 years) (62). Their analysis results demonstrated that *REST*-rs1277306 was linked with cognitive aging, which was measured by MMSE scores (62). This prediction is further supported by evidence that the association remained significant for individuals without *APOE* ε4 allele after Bonferroni correction (62). On the other hand, the *REST* rs1277306 SNP was not a predicting factor for cognitive aging among individuals with at least one *APOE* ε4 allele (62). In addition, Lin et al. tracked down an SNP–SNP interaction between the *REST* rs1713985 and *REST* rs1277306 SNPs on cognitive aging by using the GMDR. The REST protein is indicated in the modulation of synaptic plasticity, ion channels, vesicular transport, axonal growth, and neuronal differentiation (63, 64). In addition, *REST* is associated with amyloid β-protein toxicity, protection from oxidative stress, AD pathology, MCI, brain aging, and slow hippocampal loss (65–67). Additionally, *REST* might act as both a primary protector against neurodegeneration and an essential repressor for normal neurogenesis (65–67). Although *APOE* is well-established regarding its major role in cognitive decline in elder adults (68, 69), the biologically synergistic effects between the *APOE* and *REST* genes on cognitive aging are still unknown. It was speculated that *APOE* and *REST* might involve in a comparable pathway relevant to cognitive aging (70). Consistent with the findings by Lin et al. (62), several other studies pinpointed an interaction of *APOE* with *PSEN2* (71), *PSEN1* (72), *PICALM* (70), and *APP* (71, 73) by using patient stratification based on *APOE* ε4 status.

DNA Methylation

Recent studies indicate that DNA methylation, one of main epigenetic mechanisms, plays a crucial role in cognitive aging (74, 75). DNA methylation involves the inclusion of a methyl group to the DNA molecule, especially when a cytosine is followed by a guanine (76). DNA methylation is regularly associated with reduced transcriptional activity and is triggered by a family of DNA methyl-transferase proteins (77). Using repeated measures of composite scores for annual cognitive testing, Chouliaras et al. investigated associations among common SNPs in genes modulating DNA methylation and cognitive aging. They found that the rs11887120 SNP in the *DNMT3A* gene was associated with annual decline in cognitive deficits for normal aging in a Dutch population (78). In contrast, this finding was not replicated

in German subjects (79). *DNMT3A*, encoding a DNA methyltransferase, is located in the cytoplasm and nucleus in *de novo* methylation (80).

TOMM40

With longitudinal cognitive ability data, a GWAS study reported that the rs2075650 SNP in the *TOMM40* gene, which is adjacent to the *APOE* gene, was significantly associated with age-related cognitive decline (mean age: 64.6~79.1 years) (81). After fine SNP mapping of the *TOMM40*/*APOE* region, both *APOE* rs429358 and *TOMM40* rs11556505 were correlated with cognitive aging (81). Furthermore, SNPs within the *TOMM40*/*APOE* zone possessed a non-protein-coding regulatory and functional effect in a functional genomic analysis, indicating that the *TOMM40*/*APOE* zone may be linked with nonpathological cognitive aging (81). The *TOMM40* gene, located on chromosome 19q13.32, encodes the mitochondrial outer membrane complex relevant to the channel-forming subunit of the translocase, which is indispensable for construction of protein precursors to mitochondria (82).

Other Potential Genes

The *DTNBP1* gene encodes a protein that plays a role in the biogenesis of organelle linked with lysosomes, platelet dense granules, and melanosomes (83). It has been suggested that the *DTNBP1* gene modulates general cognitive abilities both in schizophrenia patients and in healthy subjects in Japanese (mean age: 34.1~39.2) and German (mean age: 24.8) populations (84–87). In addition, Burdick et al. found that the CTCTAC risk haplotype of 6 SNPs including rs909706, rs1018381, rs2619522, rs760761, rs2619528, and rs1011313 in the *DTNBP1* gene was associated with general cognitive ability and cognitive decline in schizophrenia patients (84).

In a recent systems genetics study applying a genetically diverse population of mice, Neuner et al. pinpointed *Hp1bp3* gene to be a novel modulator of cognitive aging (88). Their findings also confirmed that as compared to cognitively healthy individuals, levels of HP1BP3 protein were significantly decreased in the hippocampi of elderly subjects with cognitive impairment, suggesting that reduced expression of *Hp1bp3* may contribute to cognitive aging in both mice and humans (88). The *HP1BP3* gene is located on chromosome 1p36.12 and encodes a histone H1 related protein with non-redundant and specific roles vital for viability and gain in humans (89).

It is worth mentioning a potential gene called *SRR* although, to our knowledge, there are only animal studies but no population studies for this gene in cognitive aging. *SRR* encodes the serine racemase enzyme which converts L-serine to D-serine. D-serine is an endogenous co-agonist for N-methyl-D-aspartate receptors (90). The *SRR* rs408067 SNP, located in the promoter region, may affect the transcription activity of the *SRR* gene (91). Reduced *SRR* expression impaired hippocampal age-related cognitive function in an animal study, suggesting that the *SRR*-dependent pathway might be one possible target of the hippocampus-related cognitive decline in aging (92). Another expression profiling study reported that various genes that are associated with cognitive ability were influenced by the *SRR* mutation (93).

LIMITATIONS IN CURRENT STUDIES

Notwithstanding, there were several limitations with respect to the aforementioned studies. First, there is certainly room for development of much further research and comprehensive evaluation to reassess whether the current results remain in other ethnic populations for the investigated genetic variants with cognitive aging in terms of the association and interactions (62).

Second, given the relatively young mean age of the sample in several studies mentioned previously, the current results are unable to be extrapolated to much older populations that have higher risk for developing age-associated diseases and neurodegenerative disorders, such as MCI, AD, and other dementias (18).

Because of logistical and ethical matters, it is challenging to assess homogeneous genetic backgrounds and recruit a large enough cohort of participants at the same time (94). Furthermore, some findings were not replicated, and the discordant results found among these studies may be due to issues in the sample size, ethnicities, study design, and phenotype definitions. Moreover, confounding factors may not be fully handled, and thereby considerable bias may not be excluded.

In order to reinforce the statistical findings, it is appealing to seek more supplementary biologically relevant evidences owing to the fact that the investigated SNPs might be greatly enhanced in association studies (95).

Besides, the aforementioned studies utilized various methods to assess cognitive function. A major challenge is to ensure a proper approach for evaluating cognitive function. The well-established MMSE approach is chosen to evaluate cognitive function in several aforementioned studies because it is the most widely used screening test of cognition (96). Nevertheless, the ceiling effect of MMSE in healthy young subjects as well as its floor effect in the oldest subjects diminishes the variability (96). Similar to MMSE, another strategy is the General Practitioner Assessment of Cognition (GPCOG) with psychometric properties. However, using the GPCOG is required to further examine for its possible language or cultural tendency (97, 98). Another more recent language independent method is the CANTAB, a visual and cognitive assessment tool used on computers (99). Nonetheless, because the correlations between CANTAB and commonly used cognitive tools such as GPCOG and MMSE are only modest, the application of CANTAB should be justified in future studies (100). Moreover, an alternative is the ADAS-Cog which achieves higher sensitivity with a change of four-point (101). Although the ADAS-Cog is a well-validated scale in cognitive performance, the drawback is that about 40 min is needed to complete the task and this fact causes it unacceptable in most large-scale studies (96).

Cross-sectional design for cognitive aging studies has been adopted by many researchers because it is less feasible to examine aging trajectories for individual participants with longitudinal studies due to the high cost and long follow-up time (102). Nevertheless, it is always important to recognize the limitations of transversal studies on aging. Most importantly, we are unable to make longitudinal or causal inferences about changes in cognitive function by using cross-sectional data.

FUTURE OUTLOOK

Over the past decade, advances in genome science have spawned numerous lines of research into precision medicine and multi-omics (103). In spite of spectacular progress in precision medicine and multi-omics technology, which can assemble a mammoth amount of multi-omics data, there are no established approaches to take advantage of that data in a predictive fashion (103). Therefore, we face a challenge of developing a fundamental, personalizable, mathematical model, which is calibrated on a broad range of multi-omics and clinical data (103). To conquer this challenge, a key component of future projects is to be able to advance the aforementioned predictive capability by facilitating machine learning and predictive approaches (103).

Building up a set of genetic biomarkers which are immensely dependable as a benchmark of disease status or drug response for cognitive aging will be considerably indispensable in the future (104). At this juncture, no genetic biomarkers found in the aforementioned studies would be unquestionably qualified to be incorporated in the panel owing to the aforementioned limitations (104).

Moreover, machine learning and predictive techniques such as Bayesian networks may present a conceivable approach to forecast novel drug efficacy and establish statistical models for predicting disease status (103). In future research, we will be able to help physicians in the prescription by creating predictive models which forecast the likelihood of diseases or treatment response (103, 104). In addition, predictive and machine learning approaches such as Bayesian networks might be important in weighing correlations in RNA–RNA molecule, correlations between miRNA and mRNA, as well as interactions between gene and environment (105). Moreover, the statistical modeling such as meta-analysis, pathway analysis, and gene–gene expression correlations is intrinsic to eliminate the false positive biomarkers observed during the association analyses of current precision medicine studies (105).

Essentially, evidence shows that multi-omics data and biomarkers such as genetic, epigenetic, metabolomic, transcriptomic, and proteomic profiles are important in assorted pathophysiology for a certain disease and novel drug treatment (103, 105). Subsequently, the systematic and integrative analyses of different profiles with apparently cooperative functions might have a big impact on the disclosing for the mysterious pathogenic processes of a certain disease and novel drug treatment (103, 105–107). Finally, in order to unquestionably carry out disease pathogenesis as well as novel drug therapy, future studies will have to accomplish an integrative and systematic way of using clinical information, biomarkers, and multi-omics data (103, 105).

SUMMARY

In this review, we have focused primarily on recent findings and relevant studies for age-related cognitive decline. The current review also highlighted the merit of association studies with relatively large sample size to incorporate a wide variety of populations for cognitive aging. In order to advance personalized treatment and prevention strategies worldwide, a main challenge is how best to integrate these findings with other pieces until the picture of cognitive aging is adequately apparent. Similarly, these findings have indicated that machine learning and predictive tools might be beneficial for clinical decision making by integrating multi-omics data and biomarkers.

In light of recent developments, novel machine learning and predictive algorithms will be the new frontier in the decades to come for establishing prognostic and diagnostic assessments by using huge data technologies for precision medicine (103, 105). Future research using machine learning and predictive approaches is warranted in the matter of managing the interactions of biomarkers and foretelling the relationship between biomarkers and drug response in precision medicine studies (103, 105). In our opinion, yet a number of challenges remain and a host of deeply key and crucial research issues must be ironed out. As we enter a period of the new envisioned science of precision medicine, personalized therapy for individuals would undoubtedly become a reality.

AUTHOR CONTRIBUTIONS

EL, H-YL, and C-HL involved in conception and design; EL and C-HL involved in literature review and interpretation, and manuscript writing; EL, H-YL, and C-HL involved in financial support and final approval of manuscript.

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Right Frontotemporal Cortex Mediates the Relationship between Cognitive Insight and Subjective Quality of Life in Patients with Schizophrenia

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Although prior studies identified a relationship between cognitive insight and subjective quality of life (QOL) in patients with schizophrenia, the brain regions mediating this relationship remain unknown. Recent studies have shown that the ventrolateral prefrontal cortex may be particularly important for cognitive insight in individuals with schizophrenia. Here, we examined whether frontotemporal function mediates the relationship between cognitive insight and QOL in 64 participants, including 32 patients with schizophrenia and 32 healthy controls. Cognitive insight was measured using the Beck Cognitive Insight Scale (BCIS), while participants' subjective QOL was assessed using the Medical Outcomes Study 36-item Short-form Health Survey. Frontotemporal function was evaluated during a verbal fluency task using multichannel near-infrared spectroscopy. Consistent with previous findings, we found that frontotemporal function was impaired in patients with schizophrenia. Interestingly, our data also revealed that the right ventrolateral PFC and the right anterior part of the temporal cortex significantly mediated the relationship between the self-reflectiveness (SR) subscale of the BCIS and subjective QOL. These findings suggest that cognitive insight, particularly SR, is associated with subjective QOL in patients with schizophrenia *via* right frontotemporal function. The findings of this study provide important insight into a QOL model of schizophrenia, which may guide the development of cost-effective interventions that target frontotemporal function in patients with schizophrenia.

Keywords: cognitive insight, near-infrared spectroscopy, verbal fluency task, frontotemporal function, quality of life, schizophrenia

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INTRODUCTION

Previous research has demonstrated that individuals with schizophrenia tend to show a lack of insight that affects their symptom, psychosocial functioning, and treatment outcomes (1, 2). However, in 2004, the definition of insight was extended to include the cognitive processes that are involved in patients' re-evaluation of their anomalous experiences and misinterpretations (3, 4). Beck and colleagues (3, 5) referred to this as cognitive insight, and further identified two underlying components, namely self-reflectiveness (SR) and self-certainty (SC). To examine these factors, the Beck Cognitive

Insight Scale (BCIS) was developed (3), which revealed that when the scores for SR are low or when those for SC are high, then an individual's overall cognitive insight ability is likely impaired.

Since the development of the BCIS, many studies have evaluated the relationship between the BCIS scores and delusions (3, 5, 6), while others have examined the relationship between the BCIS scores and anxiety (7), depression (8), negative symptoms (9, 10), and functional outcome (11–13). However, recently, interest in research on the neural correlates of cognitive insight in patients with schizophrenia has been increasing (14). Studies on this topic suggest that the ventrolateral prefrontal cortex (VLPFC) may be particularly important for cognitive insight in individuals with schizophrenia (14). For instance, higher SR has been linked to increased neural activation in the right ventrolateral PFC of individuals with schizophrenia (15). Moreover, in a previous near-infrared spectroscopy (NIRS) study performed in our laboratory, we found that SR modulated right ventrolateral PFC and right temporal functions during verbal fluency task (VFT) in people with schizophrenia (16). Interestingly, we also revealed that the ventrolateral PFC and other PFC regions played a significant role in the subjective quality of life (QOL) of individuals with schizophrenia (17, 18). These findings suggest that ventrolateral PFC function may mediate the relationship between cognitive insight and subjective QOL in schizophrenia. However, this hypothesis has not been fully examined.

Near-infrared spectroscopy is a comparably new neuroimaging technique that has received increasing attention in the field of neuroscience and psychiatry. NIRS is a non-invasive, high time resolution (0.1 s) functional optical technique revealing the spatiotemporal characteristics of brain functioning by using near-infrared light (19, 20). In contrast to other neuroimaging methodologies such as functional magnetic resonance imaging (fMRI) and electroencephalography (EEG), NIRS can be measured under a more restraint-free environment that is especially suitable for psychiatric patients. This has made it feasible to perform NIRS in real-world clinical settings (21). In NIRS, typical cortical activation represents not only decreased concentration of deoxy-hemoglobin (deoxy-Hb), which is considered the main source of blood oxygenation level-dependent (BOLD) contrast increase in fMRI, but also a relatively larger increase in oxy-hemoglobin concentration (oxy-Hb) (21). NIRS measurement during a VFT was recently approved by the Ministry of Health, Labor, and Welfare of Japan as an advanced medical technology for the aid of differential diagnosis of depressive state psychiatric illnesses and has been frequently applied in clinical settings in Japan (21). In addition, several reports suggest that the mean oxy-Hb changes induced by a VFT in patients with schizophrenia are significantly decreased compared with those observed in controls (22–26).

Cognitive insight has been found to predict positive gains in individuals undergoing psychotherapy for psychosis, and improvements in cognitive insight have been correlated with improvements in delusional beliefs (12, 27). However, better cognitive insight has also been linked to negative outcomes (8, 28, 29). Weintraub and Weisman de Mamani (30) recently suggested that cognitive insight might have a similarly equivocal relationship with subjective QOL in a subclinical sample, although the exact nature of the relationship between cognitive insight and subjective QOL for patients with schizophrenia has yet to be determined.

To examine these issues, we concurrently assessed frontotemporal function, cognitive insight, and subjective QOL in patients with schizophrenia. Our three hypotheses were as follows: (1) relative to healthy controls, patients with schizophrenia would have detectable abnormalities in VFT-related frontotemporal function; (2) cognitive insight would be related to the observed frontotemporal (specifically the right) function and subjective QOL; and (3) right frontotemporal function would mediate the relationship between cognitive insight and subjective QOL.

MATERIALS AND METHODS

Participants

This study was approved by the Ethics Committee of Tottori University Faculty of Medicine (approval No. 885), and the investigation was conducted in accordance with the latest version of the Declaration of Helsinki. Written informed consent was obtained from each participant after the study procedures had been explained.

The participants included 32 patients with schizophrenia who were clinically stable enough to undergo the assessments and 32 age- and gender-matched healthy controls (**Table 1**). All the patients were receiving second-generation antipsychotic medication during the study, and their chlorpromazine-equivalent daily doses were calculated and are shown in **Table 1** (monotherapy/two drugs therapy: 28/4; 10 aripiprazole, 8 blonanserin, 8 olanzapine, 3 risperidone, 3 perospirone, 2 paliperidone, 2 quetiapine). The patients were recruited from the outpatient population of Tottori University Hospital and were diagnosed by the same experienced psychiatrists (Masaaki Iwata and Koichi Kaneko) using the criteria specified in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (31). On the day of the NIRS experiment, patients' psychiatric symptoms were evaluated by the same psychiatrists (Masaaki Iwata and Koichi Kaneko) using the Positive and Negative Syndrome Scale (32).

All participants were right-handed according to the Edinburgh Handedness Inventory (33). The participants in this study partially overlapped with those in our previous studies (16–18), but were not identical.

Assessments

Cognitive Insight

Cognitive insight was assessed with the BCIS (3, 10), a 15-item self-report inventory. The BCIS consisted of the following two components: SR and SC. The former includes items measuring objectivity, reflectiveness, and openness to feedback, whereas the latter measures the certainty about one's own beliefs or judgment. The BCIS was administered to only the patients.

Subjective QOL Measurement

All patients completed a self-assessment of QOL using the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36)

TABLE 1 | Demographics and clinical characteristics of the participants.

	Patients with schizophrenia (mean ± SD)	Healthy controls (mean ± SD)	Comparison between groups
Sex, *n* (female/male)	32 (24/8)	32 (21/11)	$\chi^2 = 0.674$, $p = 0.412$
Age, years	31.3 ± 9.8	31.9 ± 10.9	$t(df = 62) = 0.253$, $p = 0.801$
Handedness	96.7 ± 13.0	97.7 ± 10.8	$t(df = 62) = 0.334$, $p = 0.739$
Education, years	13.7 ± 2.2	14.7 ± 2.2	$t(df = 62) = 1.822$, $p = 0.073$
Estimated premorbid IQ	98.6 ± 9.4	100.3 ± 8.3	$t(df = 62) = 0.744$, $p = 0.460$
Duration of illness, years	9.7 ± 6.8	–	–
Chlorpromazine-equivalent dose, mg/day	488.9 ± 315.9	–	–
PANSS			
Positive	13.8 ± 4.0	–	–
Negative	18.1 ± 5.3	–	–
General psychopathology	31.6 ± 9.1	–	–
Number of words generated	11.9 ± 3.7	14.3 ± 3.8	$t(df = 62) = 2.496$, $p = 0.015$
BCIS			
Self-reflectiveness	11.2 ± 3.7	–	–
Self-certainty	5.3 ± 3.1	–	–
SF-36			
Physical functioning	46.8 ± 13.7	–	–
Role limitations—physical	38.1 ± 15.6	–	–
Bodily pain	48.1 ± 12.7	–	–
General health	40.6 ± 12.8	–	–
Vitality	41.6 ± 12.9	–	–
Social functioning	42.9 ± 14.6	–	–
Role limitations—emotional	36.1 ± 15.2	–	–
Mental health	40.7 ± 12.6	–	–

df, degrees of freedom; IQ, intelligence quotient; PANSS, Positive and Negative Symptom Scale; BCIS, Beck Cognitive Insight Scale; SF-36, Medical Outcomes Study 36-item Short-Form Health Survey.

(34, 35). The SF-36 is scored such that 8 scale scores are given: physical functioning, role physical, bodily pain, general health perceptions, vitality, social functioning, role emotional, and mental health. The SF-36 Scoring Manual (36) does not provide support to calculate a single measure of health-related QOL, such as an "SF-36 Total/Global/Overall Score." Therefore, we only adopted the subscale scores, which were transformed to make a minimum and maximum possible score of between 0 and 100, where higher scores indicate better health and well-being.

NIRS Measurements (37)

The 52-channel NIRS machine measures relative changes in oxy-hemoglobin (oxy-Hb) and deoxy-hemoglobin (deoxy-Hb) using two wavelengths (695 and 830 nm) of infrared light based on the modified Beer–Lambert law (37, 38). The arrangement of the source-detector probes enabled us to measure the Hb values from both the PFC and temporal regions(39, 40).

Cognitive Task

The task procedure used in this study was similar to that described by Takizawa et al. (24) in that Hb changes were measured during a letter version of the VFT. When performing the task, the participant sat on a comfortable chair and was instructed to minimize movements, such as head movements, jaw clenching, and eye blinking, to avoid producing artifacts during the NIRS measurements. The 160-s block-design VFT was divided into the following three periods: 30-s pre-task period, 60-s task period, and 70-s post-task period. The total number of correct words generated during the VFT was adopted as a measure of task performance (16).

The 160-s block-design VFT contains three different time periods: a 30-s pre-task period, a 60-s task period, and a 70-s post-task period (**Figure 1**). For the pre- and post-task baseline periods, the subjects were instructed to consecutively repeat the five Japanese vowels ("a," "i," "u," "e," and "o") aloud. As readout from NIRS, the contrast between the verbal fluency condition and the vocalization condition was used to increase specificity for the verbal fluency canceling out the vocalization effect. During the task period, they were instructed to generate as many Japanese words beginning with a designated syllable as possible. The three sets of initial syllables (A; /to/, /se/, /o/, B; /a/, /ki/, /ha/, C; /na/, /i/, /ta/) were presented in counterbalanced order among the subjects and each syllable changed every 20 s during the 60-s task.

The sampling frequency was 10 Hz. To examine VFT task-related activation, data were analyzed using the "integral mode" installed on the NIRS machine, in which the pre-task baseline was calculated as the mean over the 10-s period immediately prior to the task period, and the post-task baseline was calculated as the mean over the 5-s period that followed after the 50-s post-task period. Linear fitting was applied to the data recorded between these two baselines. A moving-average method, using a 5-s window, was applied to remove any short-term motion artifacts. In addition, we rejected noise related to body-movement artifacts (no signal, high frequency, and low frequency) using the algorithm published by Takizawa et al. (21).

Regions of Interest

We defined each measuring area between pairs of source-detector probes as "channel." It is supposed that the NIRS machine, in which the source-detector spacing is 3.0 cm, measures points at 2–3 cm depth from the scalp, i.e., the surface of the cerebral cortex

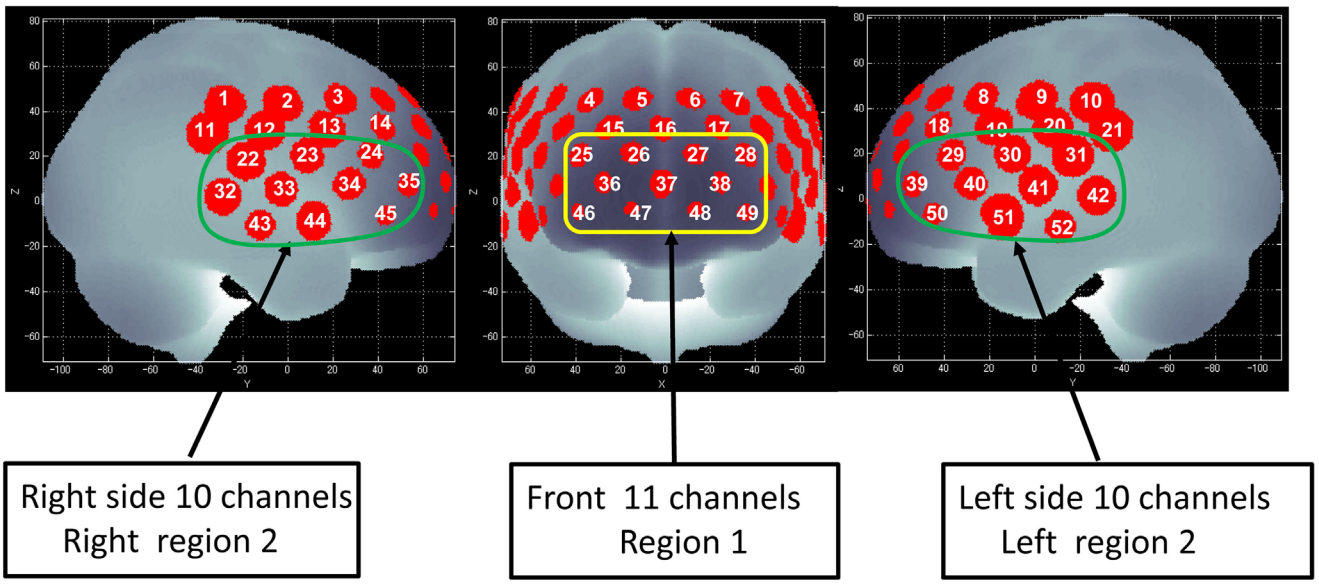

FIGURE 1 | Channel positions on the brain surface. Right region 2 consists of the right 10 channels (22–24, 32–35, and 43–45) and is located approximately on the right ventrolateral prefrontal cortex (VLPFC) and anterior part of the temporal cortex (aTC) region. Left region 2 consists of the left 10 channels (29–31, 39–42, and 50–52) and is located approximately on the left VLPFC and aTC region. Region 1 consists of the center 11 channels (25–28, 36–38, and 46–49) and is located approximately on the dorsolateral prefrontal cortex (DLPFC) and frontopolar cortex (FPC) region (45).

(41–43). The probes of the NIRS machine were fixed with thermoplastic 3 × 11 shells, with the lowest probes positioned along the Fp1–Fp2 line according to the international 10–20 system used in EEG. The 52 measuring areas are labeled ch1–ch52 from the right-posterior to the left-anterior.

Of the 52 NIRS channels, region 1 included channels 25–28, 36–38, and 46–49. The right side of region 2 included channels 22–24, 32–35, and 43–45, while the left side of region 2 included channels 29–31, 39–42, and 50–52 (**Figure 1**). The NIRS signal of region 1 consisted of the signals from channels located approximately in the dorsolateral PFC and frontopolar cortex (FPC) [dorsolateral prefrontal cortex (DLPFC)/FPC; i.e., the superior and middle frontal gyrus]. Region 2 consisted of signals from channels located approximately in the ventrolateral PFC and the anterior part of the temporal cortex (VLPFC/aTC) (21, 44, 45).

Statistical Analysis

Statistical analyses were performed using SPSS Statistics 24.0 (IBM Corporation, Armonk, NY, USA). Hemodynamic responses during the VFT in region 1 and left and right region 2 were assessed by the "integral value" of Hb changes. We used the integral value of the oxy-Hb (as opposed to deoxy-Hb) changes that occurred during the VFT, as an index of cortical activity, because oxy-Hb better reflects this activity and is better correlated with fMRI BOLD signals (46–48) compared with deoxy-Hb.

First, the integral value of the oxy-Hb changes that occurred during the task period were compared between the participant groups using Student's *t*-tests [with a Bonferroni-corrected alpha level of 0.0167 (0.05/3)]. When there was a significant between-group difference in the performance level, we performed additional analyses of covariance using the performance level as a covariate to the integral value of oxy-Hb changes. Next, Pearson's product–moment correlation coefficients adopting the false discovery rate (FDR) method were calculated to test the correlations between the integral value of oxy-Hb changes in each region of interest (ROI; region 1 and left and right region 2) and the BCIS subscale scores (SR and SC) and SF-36 subscale scores.

A mediation analysis was performed using Hayes' PROCESS macro, a regression-based path analysis technique (49). Using an ordinary least-squares framework, PROCESS estimates the direct and indirect effects in mediator models. To test the mediation hypotheses, PROCESS uses bootstrapping to construct confidence intervals (CIs) for indirect effects through repeated sampling of the data set. Findings are based on 5,000 bias-corrected bootstrapped samples. In the event that 0 does not lie within the 95% CI for the bootstrapped results for indirect effects, we can conclude that the indirect effect is significantly different from 0 and that mediation is demonstrated (50).

RESULTS

The participants' demographic data are shown in **Table 1**. Patients with schizophrenia had a significantly lower performance level on the VFT (number of words generated) compared with healthy controls ($t = 2.496$, $p = 0.015$).

Frontotemporal Activation

We used NIRS to evaluate our first hypothesis that patients with schizophrenia would have abnormalities in frontotemporal regions. The overall mean oxy-Hb change waveforms for the 52 channels and three ROIs in each group are shown in **Figure 2**. Compared with healthy controls, patients with schizophrenia exhibited

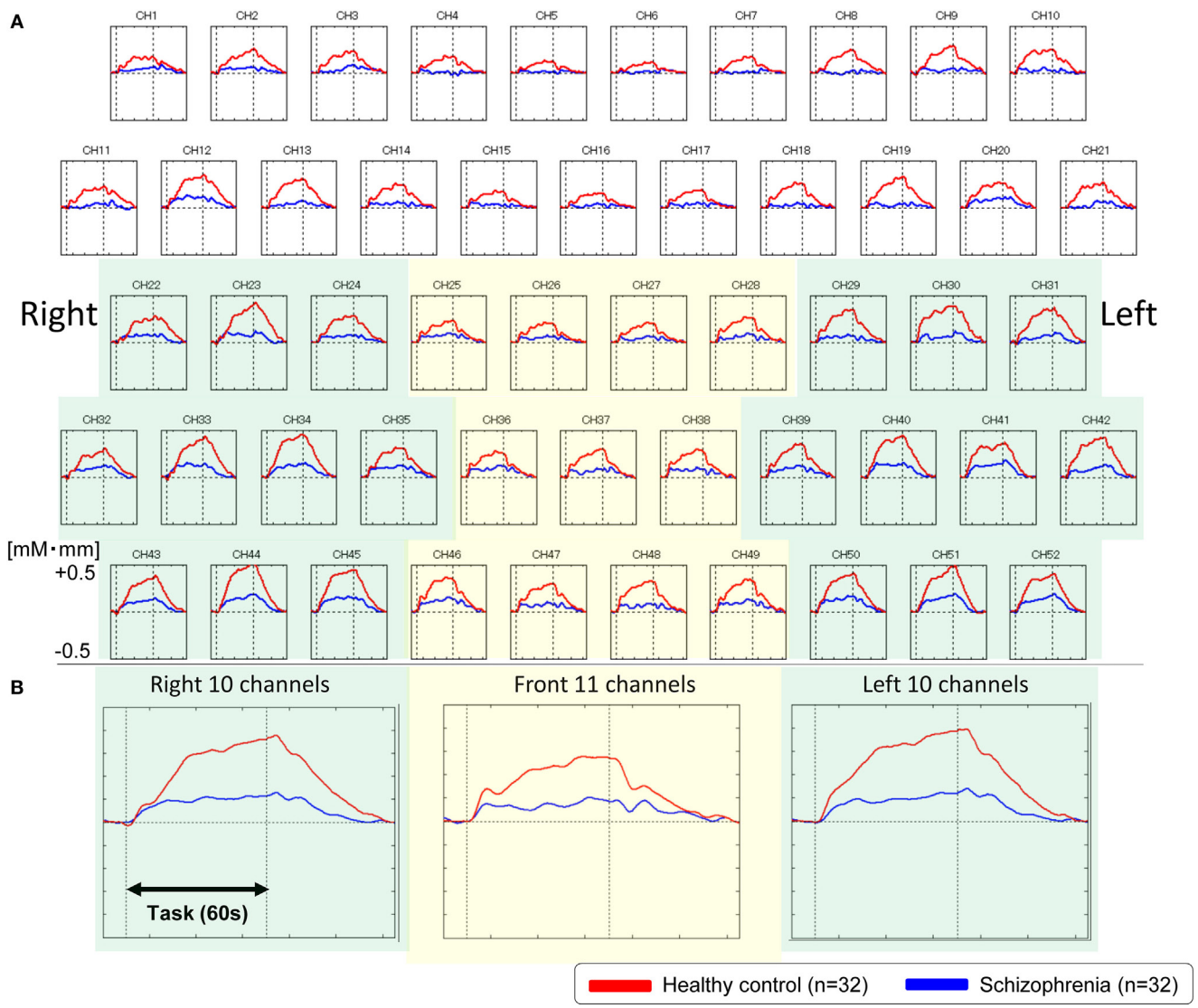

FIGURE 2 | Waveforms of oxygenated-hemoglobin (oxy-Hb) concentration changes during the VFT. **(A)** The upper figures show the overall average waveforms of concentrations of oxy-Hb changes during the VFT in patients with schizophrenia (blue) and healthy controls (red). **(B)** In the lower three figures, the right figure shows the average waveforms of oxy-Hb changes for the 10 channels in the right VLPFC/aTC region, the center figure shows the average waveforms of oxy-Hb changes for the 11 channels in the frontal pole region, and the left figure shows the average waveforms of oxy-Hb changes for the 10 channels in the left VLPFC/aTC region. Abbreviations: VLPFC, ventrolateral prefrontal cortex; aTC, anterior part of the temporal cortex; VFT, verbal fluency task.

significantly smaller integral values of oxy-Hb changes (region 1: $t = 4.177$, $p < 0.001$; left region: $t = 4.923$, $p < 0.001$; right region 2: $t = 4.027$, $p < 0.001$). The between-group differences in the integral values of oxy-Hb changes remained significant after correcting for the performance level in the three ROIs (region 1: $F = 14.907$, $p < 0.001$; left region: $F = 21.261$, $p < 0.001$; right region 2: $F = 14.327$, $p < 0.001$), according to analyses of covariance using performance on the VFT as a covariate to the integral values of oxy-Hb changes.

Correlation Analyses

Next, we examined whether cognitive insight was related to frontotemporal function and subjective QOL in patients with schizophrenia. To test this hypothesis, we extracted the integral values of oxy-Hb changes from the three ROIs (region 1 and left and right region 2), where patients with schizophrenia showed reduced VFT-related neural activity compared with healthy controls, and conducted Pearson's correlations with the cognitive insight and subjective QOL scores (**Table 2**).

In patients with schizophrenia, better cognitive insight, according to the SR subscale of the BCIS was related to a higher subjective QOL (vitality: $r = 0.411$, FDR-corrected $p = 0.013$; mental health: $r = 0.508$, FDR-corrected $p = 0.006$) and to increased right region 2 VFT-related activity (right VLPFC/aTC; $r = 0.506$, FDR-corrected $p = 0.017$). A higher subjective QOL was also related to increased VFT-related activity in region

TABLE 2 | Correlations between the VFT-related hemodynamic responses and measures of cognitive insight and subjective QOL in patients with schizophrenia.

	Cognitive insight		Region 1 (DLPFC/FPC)	Left region 2 (left VLPFC/aTC)	Right region 2 (right VLPFC/aTC)
	Self-reflectiveness	Self-certainty			
Frontotemporal region					
Region 1 (DLPFC/FPC)	0.337	−0.100	–	–	–
Left region 2 (left VLPFC/aTC)	0.273	0.011	–	–	–
Right region 2 (right VLPFC/aTC)	0.506***	−0.163	–	–	–
Subjective QOL					
Physical functioning	−0.171	0.079	0.128	0.135	0.060
Role limitations—physical	0.043	−0.075	0.050	0.072	0.188
Bodily pain	0.020	−0.312	0.117	0.239	0.232
General health	0.121	−0.241	0.287	0.392*	0.378
Vitality	0.411*	−0.057	0.495***	0.492*	0.501***
Social functioning	0.226	−0.082	0.301	0.222	0.120
Role limitations—emotional	0.183	−0.094	0.213	0.168	0.080
Mental health	0.508***	−0.047	0.320	0.461**	0.509***

VFT, verbal fluency task; QOL, quality of life; DLPFC/FPC, dorsolateral prefrontal cortex and frontopolar cortex; VLPFC/aTC, ventrolateral prefrontal cortex and the anterior part of the temporal cortex.
**p < 0.05.*
***p < 0.01.*
****p < 0.005.*

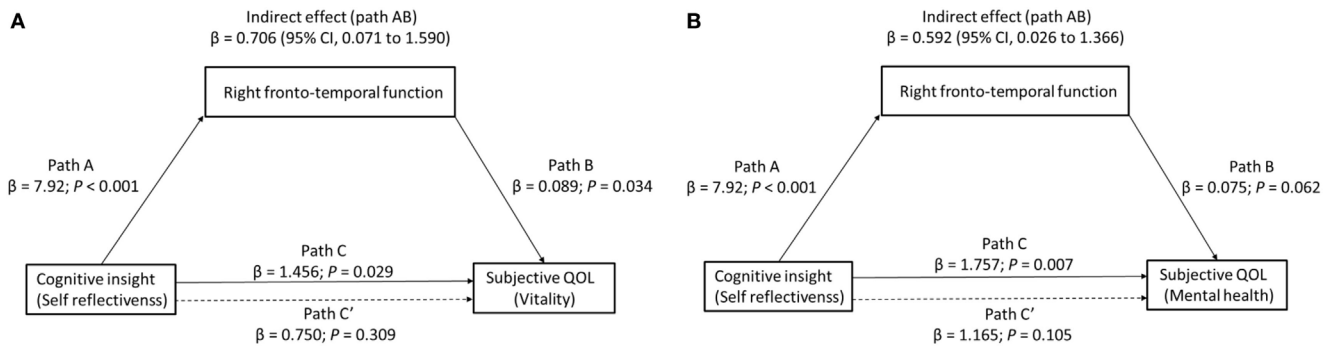

FIGURE 3 | The effect of cognitive insight on subjective quality of life (QOL) through right frontotemporal function. Path C represents the variance in the level of cognitive insight that is associated with the subjective QOL (**(A)** vitality or **(B)** mental health) level, and Path C′ represents the association between the level of cognitive insight and subjective QOL after taking into account right frontotemporal function as a mediator. When right frontotemporal function was included in the model, the direct effect of cognitive insight (self-reflectiveness) on subjective QOL (dashed line) (left: vitality, right: mental health) was no longer significant, indicating a fully mediated effect. Path AB is the mediation effect and is significant at $p < 0.05$ based on confidence intervals from bias-corrected bootstrapping of 5,000 samples.

1 (DLPFC/FPC; vitality: $r = 0.495$, FDR-corrected $p = 0.006$), left region 2 (left VLPFC/aTC; vitality: $r = 0.492$, FDR-corrected $p = 0.006$; mental health: $r = 0.461$, FDR-corrected $p = 0.013$), and right region 2 (right VLPFC/aTC; vitality: $r = 0.501$, FDR-corrected $p = 0.013$; mental health: $r = 0.509$, FDR-corrected $p = 0.006$), but neither region 1 ($r = 0.273$, FDR-corrected $p > 0.50$) nor left region 2 ($r = 0.337$, FDR-corrected $p > 0.05$) were related to SR.

However, there were no significant correlations between the SC and other subscale of QOL or all ROIs VFT-related activity (FDR-corrected $p > 0.05$).

Mediation Analyses

Finally, we determined whether right frontotemporal function mediated the relationship between cognitive insight and subjective QOL. Because the vitality and mental health subscales were found to relate to both right region 2 (right VLPFC/aTC) VFT-related activity and our measure of cognitive insight (SR), to test our third hypothesis that right VLPFC/aTC function mediates the relationship between cognitive insight and subjective QOL, we entered right VLPFC/aTC VFT-related activity, SR, and vitality or mental health scores into a single mediator model. For the mediation analysis to be justified, the predictor, mediator, and outcome variables must all be inter-related (51, 52). Indeed, all four paths were in the predicted direction (**Figure 3**). Cognitive insight had a positive effect on subjective QOL (vitality: $\beta = 1.456$, $p = 0.029$; mental health: $\beta = 1.757$, $p = 0.007$) and right region 2 VFT-related activity ($\beta = 7.920$, $p < 0.001$), and right region 2 VFT-related activity had a positive effect on subjective QOL (vitality: $\beta = 0.089$, $p = 0.034$; mental health: $\beta = 0.075$, $p = 0.062$). Bootstrap analysis of the indirect

effect revealed bias-corrected CIs excluding 0 (vitality: $\beta = 0.71$, SE = 0.39, 95% CI = 0.071–1.59; mental health: $\beta = 0.59$, SE = 0.33, 95% CI = 0.03–1.37). Importantly, the direct effect of cognitive insight on subjective QOL, after controlling for right VLPFC/aTC function, was no longer significant (vitality: $\beta = 0.75$, 95% CI = −0.730 to 2.229; mental health: $\beta = 1.17$, 95% CI = −0.259 to 2.589), indicating that right VLPFC/aTC function fully mediated the relationship between cognitive insight in the SR domain and subjective QOL.

DISCUSSION

This study had three main findings. First, we identified regions within our selected frontotemporal area (all ROIs) where participants with schizophrenia had reduced hemodynamic responses compared with healthy controls. This finding is consistent with those of prior studies (16, 22–26) and provides further evidence that patients with schizophrenia exhibit abnormalities in frontotemporal regions. Second, the level of cognitive insight as well as the level of subjective QOL were related to neural activity in the right VLPFC/aTC regions, demonstrating a relationship between the neurobiological characteristics of schizophrenia and cognitive insight and subjective QOL. Third, VFT-related neural activity in the right VLPFC/aTC regions fully mediated the relationship between cognitive insight and subjective QOL, indicating that the disease-related level of cognitive insight may affect the subjective QOL through abnormalities in frontotemporal function.

Collectively, our findings have implications for understanding the specific role the cognitive insight level (particularly SR) plays in the level of subjective QOL in individuals with schizophrenia. Recent functional (fMRI and NIRS) (16, 53) and structural MRI (54) studies highlighted the relationship between SR and the right ventrolateral PFC. SR is defined as the ability to simultaneously consider various types of information, perspectives, and alternative hypotheses to generate judgments about the self, and this ability utilizes verbal working memory and decision-making processes (16, 54). High levels of SR may encourage patients to doubt their distorted and unrealistic perceptions or thoughts, leading them to have a more-objective attitude toward their illness (55). For instance, Phalen et al. (2) (p. 840) stated that "while engaged in treatment, those patients with higher cognitive insight may be better able to incorporate the feedback of mental health professionals and consider alternative ways of thinking" (56). Trials employing cognitive behavior therapy for psychosis support this theory, as they have consistently found that better cognitive insight is predictive of better responses to psychosocial treatments (2, 27). Moreover, in decision-making, the right ventrolateral PFC plays a role generating alternative perspectives in tasks requiring individuals to respond to a problem that has various potential answers (57, 58). In the context of SR, one's willingness to admit fallibility and corrigibility and to recognize dysfunctional reasoning may in part depend on the controlled retrieval of information from memory, which is mediated by the ventrolateral PFC (15, 53). In our prior NIRS studies, we identified a relationship between the ventrolateral PFC and other PFC areas and subjective QOL in patients with schizophrenia (17, 18). Here, we found that the right VLPFC/aTC fully mediated the relationship between SR and subjective QOL, implying that this region is critical for both functions. This findings confirm our prior findings, while the results from the mediation analysis additionally demonstrate that right ventrolateral PFC function is one of the mechanisms underlying the relationship between cognitive insight (particularly SR) and subjective QOL.

Although cognitive insight is commonly considered an important factor in schizophrenia (2, 59), how cognitive insight relates to broader outcomes like QOL remains unknown. A well-replicated pattern in schizophrenia research is that higher levels of cognitive insight are often associated with better outcomes [e.g., Ref. (30, 60)]. Our findings imply that higher SR levels may be generally associated with better subjective QOL. However, this association is not necessarily consistent. Some lines of evidence suggest that superior cognitive insight is related to positive outcomes for patents with psychotic disorders (8, 12, 27), while others imply that it is associated with negative outcomes (8, 28, 29). One possible explanation for these equivocal findings is that the effect of cognitive insight on QOL depends on the presence of other variables. Recently, Phalen et al. (2) found that SR had an unmoderated positive relationship with QOL and that the effect of SC on QOL was moderated by symptom severity. The authors suggested that cognitive insight is related to QOL, but that different aspects of cognitive insight may relate to QOL in different ways (2). According to their view, it is likely that symptom severity moderates the effects of cognitive insight on QOL because the flexible perspective shifting abilities associated with better cognitive insight may differ in patients with varying levels of symptom severity (2). For patients whose symptoms are severe and obvious to others, higher SC may serve as a protective factor against the social stigma that may harm the QOL (2). On the other hand, SR may generally be associated with better QOL as noted above. However, the meta-analysis by Palmer et al. (8) supports the alternative view of Kim et al. (4) that SR is negatively associated with the level of subjective QOL. Thus, further studies are needed to clarify the relationship between SR and QOL. Overall, our findings suggest that cognitive insight (SR) is related to subjective QOL; it is possible that SR contributes to improved subjective QOL (vitality, mental health) *via* the neural activity in the right VLPFC/aTC. Additional studies are necessary to explore other possible mediating and moderating factors and to evaluate the effects that various therapeutic interventions may have on the relationship between cognitive insight and QOL.

The two subscales that showed a positive association with oxy-Hb changes, vitality and mental health, were closely related to mental aspects of QOL, which was similar to the motivation/energy subscale showing a positive relationship with left frontal and temporal gray matter volume in Ubukata et al. (61). Interestingly, executive functioning, a cognitive process involved in VFT, has been reported to show a positive relationship with different aspects of subjective QOL from those found in this study, which are self-evaluation of side-effects and symptoms (62, 63). These findings suggest a possibility that oxy-Hb changes elicited by VFT may reflect the motivation and positive engagement of the task rather than cognitive ability *per se* (18).

Our findings need to be interpreted within the context of the study limitations. First, multichannel NIRS has limited spatial resolution compared with fMRI (~1 mm). However, a recent MRI and NIRS combination study, which used a method for the probabilistic registration of NIRS data onto the Montreal Neurological Institute coordinate space, suggested that the errors of spatial estimation, expressed as SDs, were approximately 10 mm (40, 64). Second, the relationship among cognitive insight, QOL in the mental aspects and right frontotemporal activities was observed only in patients with schizophrenia, and therefore care must be taken that it cannot be applied generally to other populations.

In conclusion, this study demonstrated that the level of cognitive insight (especially SR) affected the subjective QOL level in patients with schizophrenia owing to abnormalities in VFT-related frontotemporal function. These findings improve our understanding of how the cognitive insight indicators of schizophrenia are related to the clinical and behavioral presentations of the illness.

ETHICS STATEMENT

This study was approved by the ethics committee of the Faculty of Medicine of Tottori University (approval No. 885) and the investigation was conducted in accordance with the latest version of the Declaration of Helsinki. Written informed consent was obtained from each participant after the study procedures had been explained.

AUTHOR CONTRIBUTIONS

SP, KN, and KK designed the study; SP acquired and analyzed the data; SP and KN wrote the first draft of the article; SP, KN, MSI, HO, MKI, IN, and KK contributed to the interpretation of the results and the writing of the manuscript. All authors have approved the final manuscript.

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Cognitive Function and Monoamine Neurotransmission in Schizophrenia: Evidence From Positron Emission Tomography Studies

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Positron emission tomography (PET) is a non-invasive imaging technique used to assess various brain functions, including cerebral blood flow, glucose metabolism, and neurotransmission, in the living human brain. In particular, neurotransmission mediated by the monoamine neurotransmitters dopamine, serotonin, and norepinephrine, has been extensively examined using PET probes, which specifically bind to the monoamine receptors and transporters. This useful tool has revealed the pathophysiology of various psychiatric disorders, including schizophrenia, and the mechanisms of action of psychotropic drugs. Because monoamines are implicated in various cognitive processes such as memory and executive functions, some PET studies have directly investigated the associations between monoamine neurotransmission and cognitive functions in healthy individuals and patients with psychiatric disorders. In this mini review, I discuss the findings of PET studies that investigated monoamine neurotransmission under resting conditions, specifically focusing on cognitive functions in patients with schizophrenia. With regard to the dopaminergic system, some studies have examined the association of dopamine D1 and D2/D3 receptors, dopamine transporters, and dopamine synthesis capacity with various cognitive functions in schizophrenia. With regard to the serotonergic system, 5-HT1A and 5-HT2A receptors have been studied in the context of cognitive functions in schizophrenia. Although relatively few PET studies have examined cognitive functions in patients with psychiatric disorders, these approaches can provide useful information on enhancing cognitive functions by administering drugs that modulate monoamine transmission. Moreover, another paradigm of techniques such as those exploring the release of neurotransmitters and further development of radiotracers for novel targets are warranted.

Keywords: cognitive function, schizophrenia, positron emission tomography, monoamine, dopamine, serotonin

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INTRODUCTION

Positron emission tomography (PET) is a non-invasive imaging technique used to assess various brain functions, including cerebral blood flow, glucose metabolism, and neurotransmission, in the living human brain. In particular, neurotransmission via the monoamine neurotransmitters dopamine, serotonin, and norepinephrine, has been extensively

examined using PET probes, which specifically bind to the receptors, transporters, and other target molecules of these monoamines. PET provides various aspects of neurotransmission such as presynaptic and postsynaptic functions, along with anatomical information. This useful tool has revealed aspects of the pathophysiology of various psychiatric disorders, including schizophrenia, and the mechanisms of action of psychotropic drugs since monoamines are the primary targets for antipsychotic and antidepressant drugs (1). Specifically, the differences between patients and healthy controls, associations with symptomatology and psychopathology in patients, and receptor/transporter occupancy by psychotropic drugs have been reported, albeit the results have been inconsistent among studies. Since previous animal studies and human pharmacological studies have implicated monoamines in various cognitive functions, some PET studies have directly explored the associations between monoamine neurotransmission and cognitive functions in healthy individuals and patients with psychiatric disorders.

Schizophrenia, one of the most severe and complex psychiatric disorders, with a lifetime prevalence of approximately 1% worldwide, is characterized by psychosis (positive symptoms), negative symptoms, and cognitive dysfunction (2). In recent years, cognitive impairment has been considered a core feature of this disorder (3, 4), with the largest effect sizes reported in both verbal memory and executive function (5, 6). A number of functional neuroimaging studies that measured cerebral blood flow using functional magnetic resonance imaging (fMRI) and PET have revealed a relationship between cognitive deficit and altered regional brain functions (5–9). However, not many studies have used PET to explore the relationship between monoamine neurotransmission and cognitive dysfunction in schizophrenia. In this mini review, I discuss the findings of monoamine PET studies, specifically focusing on neurocognitive functions in individuals with schizophrenia.

PET TECHNIQUES FOR EVALUATION OF MONOAMINE TRANSMISSION

Most of the radiotracers used for neuroimaging-based quantification of receptors and transporters are pharmacologically antagonists that reversibly and specifically bind to these targets. The main outcome measure is the binding potential relative to the concentration of non-displaceable radiotracer in the brain (BP_{ND}), corresponding to the ratio of the density of receptors or transporters available to bind radiotracer *in vivo* (B_{avail}) to the dissociation constant of the radiotracer (K_D) (10, 11). The gold standard of kinetic analysis of brain PET measurements is a compartment analysis with arterial input function, which requires arterial blood sampling and metabolite analysis of the parent compound. However, simplified methods can be applied if a reference region that is devoid of the receptor/transporter, such as the cerebellum, is present. These simplified methods are less invasive and more suitable for clinical use. For this review, I have selected PET studies performed under resting conditions (mainly for unmedicated individuals), which evaluate receptor/transporter availability and neurotransmitter synthesis capacity. Single photon emission computed tomography (SPECT) studies were not included because PET has a much higher sensitivity and spatial resolution than does SPECT, and more tracers have been developed for PET than for SPECT. The main PET tracers used for the measurement of central monoaminergic transmission are listed in **Table 1**. Some PET tracers have been reported to measure dopamine release, however, I did not include these challenge studies because my primary interest was to provide an overview of various monoamine transmissions in basic and simple conditions. A summary of studies that investigated both monoamine PET and cognitive functions in patients with schizophrenia and/or healthy subjects is listed in **Table 2**.

TABLE 1 | PET probes used for the measurement of central monoaminergic transmission.

Monoamine	Target	Name of PET probes
Dopamine	D1	[^{11}C]SCH23390, [^{11}C]NNC112
	D2/D3	[^{11}C]raclopride*, [^{11}C]FLB457*, [^{18}F]fallypride*
	Transporter	[^{11}C]CFT
	Synthesis	[^{18}F]DOPA, [^{11}C]DOPA
Serotonin	1A	[^{11}C]WAY100635
	2A	[^{18}F]altanserin
	Transporter	[^{11}C]DASB
Norepinephrine	Transporter	[^{18}F]FMeNER-D2

These probes can be used to measure dopamine release.

DOPAMINE

Dopamine is the main neurotransmitter involved in the pathophysiology and treatment of schizophrenia (12). Dopamine pathways have been well illustrated by PET with different radiotracers (13) and these PET tracers have been used to elucidate various aspects of aberrant dopaminergic transmission in schizophrenia for review see (14–16).

D1 Receptors

D1 receptors are densely localized in the striatum, and uniformly distributed in the neocortical regions (13). Evidence from animal and clinical research has suggested the presence of prefrontal dysfunctions in schizophrenia, and the D1 receptors in this brain region are considered to play crucial roles in various frontal lobe functions such as working memory (17–19).

Using the tracer [^{11}C]SCH23390, Okubo et al. showed that patients with schizophrenia had lower D1 availability in the prefrontal cortex (20). They examined 17 male patients with schizophrenia (10 antipsychotic-naïve and 7 antipsychotic-free) and 18 healthy male controls. Availability of the D1 receptor in the prefrontal cortex was negatively correlated with the severity of negative symptoms, and was also associated with poor performance on the Wisconsin Card Sorting Test (WCST), which assesses executive function and prefrontal function. In contrast, using the tracer [^{11}C]NNC112, Abi-Dargham et al. reported increased availability of the D1 receptor in the dorsolateral

TABLE 2 | Summary of studies that investigated both monoamine PET and cognitive functions in patients with schizophrenia and/or healthy subjects.

Study	Year	Subjects	Cognitive tasks	PET probe	Findings
Okubo et al. (20)	1997	17 with Sch and 18 HV	WCST	[^{11}C]SCH23390	Reduced prefrontal D1RA was associated with poor WCST performance
Abi-Dargham et al. (21)	2002	16 with Sch and 16 HV	N-back	[^{11}C]NNC112	Increased prefrontal D1RA was associated with poor working memory
Takahashi et al. (22)	2008	23 HV	WCST, ROCFT, RAVLT	[^{11}C]SCH23390	An inverted U-shaped relationship between prefrontal D1RA and WCST performance
Hirvonen et al. (27)	2005	11 unaffected co-twins with Sch and 7 twin HV	WMS-R, CVLT	[^{11}C]raclopride	Higher D2RA in the caudate was associated with a poor performance on tasks related to schizophrenia vulnerability
Cervenka et al. (29)	2008	16 HV	Pair associative learning, delayed pattern recognition memory, word recognition, WAIS-R, category fluency	[^{11}C]raclopride	D2RA in the limbic striatum was related to episodic memory, D2RA in the associative and sensorimotor striatum showed associations with non-episodic tasks
Vyas et al. (35)	2017	25 with Sch and 19 HV	WCST, CVLT	[^{18}F]fallypride	In individuals with Sch, D2RA was negatively correlated with WCST and CVLT performance whereas positive correlation was observed in HV
Takahashi et al. (36)	2007	25 HV	RAVLT, ROCFT, WCST	[^{11}C]FLB457	Hippocampal D2RA was positively correlated with memory and also associated with frontal lobe functions
Yoder et al. (38)	2004	10 with Sch (most were medicated)	PANSS	[^{11}C]CFT	Striatal DAT availability was inversely correlated with scores on the cognitive subscale of PANSS
Velnaleken et al. (48)	2007	11 HV	CPT, Stroop, TMT, WCST	[^{18}F]DOPA	Positive correlations between DA synthesis capacity in the caudate nucleus, putamen, and midbrain with performance on TMT-B, CPT, and Stroop test
Meyer-Lindenberg et al. (41)	2002	6 with Sch and 6 HV	WCST	[^{18}F]DOPA	Decreased PFC activation measured with fMRI predicted exaggerated striatal DA synthesis capacity
McGowan et al. (49)	2004	16 medicated individuals with Sch and 12 HV	Stroop, VF, SDMT	[^{18}F]DOPA	Negative correlations between Stroop interference scores and DA synthesis capacity in the ACC in both individuals with Sch and HV
Howes et al. (43)	2009	24 prodromal individuals with Sch, 6 with Sch, and 12 HV	VF	[^{18}F]DOPA	Within the prodromal Sch group, performance on the semantic VF task was negatively correlated with striatal DA synthesis capacity
Yasuno et al. (58)	2003	16 HV	WMS-R	[^{11}C]WAY100635	Negative correlation between explicit memory function and 5-HT1ARA in hippocampus
Borg et al. (59)	2006	24 HV	Claeson–Dahl Learning and Memory Test, CPT, spatial working memory test, ROCFT, controlled oral assessment, WCST	[^{11}C]WAY100635	No correlation between performance on any of the cognitive tests and 5-HT1ARA in the raphe, hippocampus, and neocortex
Penttila et al. (60)	2016	24 HV	WCST, WMS-R	[^{11}C]WAY100635	Global 5-HT1ARA was positively correlated with verbal memory
Rasmussen et al. (61)	2010	30 with Sch and 30 HV	Spatial working memory, Stockings of Cambridge, Intra-Extradimensional set-shifting, rapid visual information processing	[^{18}F]altanserin	No correlation between neurocognitive measures and 5-HT2ARA in any region
Madsen et al. (63)	2011	32 HV	Stroop, TMT, RAVLT, ROCFT, Intelligenz-Struktur-Test 2000 R	[^{11}C]DASB	Positive associations between 5-HTT availability and Stroop test performance and logical reasoning. No association between 5-HTT availability and memory

Sch, schizophrenia; HV, healthy volunteer; RA, receptor availability; WCST, Wisconsin Card Sorting Test; ROCFT, Rey-Osterrieth's Complex Figure Test; RAVLT, Rey's Auditory Verbal Learning Test; WMS-R, Wechsler Memory Scale-Revised; CVLT, California Verbal Learning Test; WAIS-R, Wechsler Adult Intelligent Scale-Revised; DLPFC, dorsolateral prefrontal cortex; PANSS, Positive and Negative Syndrome Scale; DAT, dopamine transporter; CPT, Continuous Performance Test; TMT, Trail Making Test; fMRI, functional magnetic resonance imaging; VF, verbal fluency; SDMT, Symbol-Digit Modality Test; ACC, anterior cingulate cortex; 5-HT1A, 5-hydroxytryptamine 1A; 5-HT2A, 5-hydroxytryptamine 2A; 5-HTT, 5-hydroxytryptamine transporter.

prefrontal cortex of 16 untreated patients with schizophrenia (7 antipsychotic-naïve and 9 antipsychotic-free) compared to that in 16 healthy subjects (21). The increased availability was related to n-back task performance, which represents working memory. The discrepancy in these results could arise owing to difference in the background of patients (age, sex, and prior exposure to antipsychotics) and the different tracers used. Additionally, the results of a study by Takahashi et al. provide a potential explanation for this discrepancy. Using [^{11}C]SCH23390 PET in healthy subjects, they found a U-shaped relationship between

prefrontal D1 receptor availability and the performance on the WCST, indicating that too little or too much D1 receptor stimulation hampers working memory or set shifting (22, 23), which was also hypothesized from the results of animal studies (18, 19).

D2/D3 Receptors

The striatum, which has dense dopamine innervation, is usually imaged using a moderate-affinity PET probe such as [^{11}C]raclopride, and extrastriatal regions with very low levels of D2/D3 receptors, including the cortex, limbic regions, and thalamus, are imaged by high-affinity PET probes such as [^{11}C]FLB457 and [^{18}F]fallypride (**Table 1**). All these tracers are benzamide derivatives and antagonistically bind to both D2 and D3 receptors.

Dopamine D2 receptors are the primary target of currently available antipsychotic drugs owing to their potential to block these receptors (1, 2). Accordingly, several PET studies have investigated dopamine D2 receptors in schizophrenia beginning from the 1980's. However, previous reviews and meta-analyses PET and SPECT studies showed no difference or a small elevation in striatal D2/D3 receptor availability in unmedicated patients with schizophrenia compared to that in healthy controls under resting conditions (15, 24–26); however, the elevation was not evident in drug-naïve patients (26). Among these studies, a few evaluated cognitive functions because most studies focused on the psychopathology, particularly positive symptoms; therefore, less attention was given to cognitive impairment involving striatal dopamine D2 receptors in schizophrenia. Using PET and [^{11}C]raclopride, Hirvonen and colleagues (27) examined 6 monozygotic and 5 dizygotic unaffected co-twins of patients with schizophrenia and 4 monozygotic and 3 dizygotic healthy control twins. They found that dopamine D2 receptor availability in the caudate was upregulated in unaffected monozygotic co-twins, and this upregulation was associated with poor performance on cognitive tasks such as a part of the Wechsler Memory Scale-Revised and the California Verbal Learning Test (CVLT).

The striatum can be divided into three functional subdivisions: the limbic, associative, and sensorimotor striatum (28). In healthy subject, using [^{11}C]raclopride PET, Cervenka et al. found a distinct pattern of correlations among the striatal subregions; D2 receptor availability in the limbic striatum was related to performance on episodic memory, while that in the associative and sensorimotor striatum showed associations to non-episodic tasks (29).

With regard to extrastriatal D2/D3 receptors, significant differences in their availability between schizophrenia and healthy controls have been reported particularly in the thalamus (30–33); a meta-analysis found the summary effect size for thalamic D2/D3 availability was $d = -0.32$, however, did not reach significance (34). In a very recent comprehensive study, Vyas et al. used [^{18}F]fallypride to evaluate executive dysfunction and memory impairment in patients with schizophrenia (35). Twenty medication-naïve and 5 drug-free patients with schizophrenia underwent the WCST and CVLT. Patients with schizophrenia showed negative or low correlations between D2/D3 receptor availability and WCST performance, while healthy subjects showed positive correlations, suggesting better performance with higher D2/D3 receptor availability; the difference was marked in the thalamus. Similarly, patients showed negative or very low correlations between D2/D3 receptor availability in the fronto-striatal-thalamic regions and performance on the CVLT, while healthy subjects showed a positive correlation. In another study in healthy subjects, Takahashi et al. reported a relationship between hippocampal dopamine D2 receptors and not only memory but also frontal functions such as executive functions and verbal fluency (36).

Dopamine Transporter (DAT)

The majority of molecular imaging studies investigating striatal DAT availability failed to find any significant differences between healthy controls and untreated patients with schizophrenia (15), and this finding was supported by the results of recent meta-analyses that included PET and SPECT studies (26, 37). One study showed that schizophrenia patients with tardive dyskinesia had lower DAT availability than schizophrenia patients without tardive dyskinesia, and that striatal DAT availability was correlated with the severity of negative symptoms, and cognitive and depression/anxiety scores on the positive and negative syndrome scale (38). However, most of the subjects in the study were medicated and the medication effect needs to be considered. In addition, no MRI scans were available for all patients, and positive and negative syndrome scale scores were not assessed for some patients. To the best of my knowledge, measures of cognitive functions were not evaluated in any other PET studies on DAT in schizophrenia.

L-DOPA Uptake (Dopamine Synthesis Capacity)

The endogenous dopamine synthesis rate is commonly measured using 6-[^{18}F]fluoro-L-DOPA or L-[β-^{11}C]DOPA, two radioactive analogs of the dopamine precursor L-DOPA, which are indicative of dopamine synthesis capacity in presynaptic terminals (13, 16). In schizophrenia compared to healthy controls, increased dopamine synthesis capacity has been consistently shown in the majority of previous studies (39–46) (for review see (15, 16)) and recent meta-analyses confirmed the findings with large effect sizes (26, 47).

In a study investigating the association between human cognitive function and dopamine synthesis capacity, Velnaleken et al. (48) found significant positive correlations in healthy subjects between the dopamine synthesis capacity in the striatum and performance on the trail-making test-B, continuous performance test, and Stroop test. In one study with unmedicated schizophrenia patients (41), PET with [^{18}F]DOPA and [^{15}O]H_2O (which measures cerebral blood flow) revealed that patients with schizophrenia had higher dopamine synthesis capacity in the striatum than healthy controls did, indicating exaggerated presynaptic dopamine function. In patients with schizophrenia, the increase in cerebral blood flow in the dorsolateral prefrontal cortex during the WCST task was tightly coupled with striatal dopamine synthesis capacity; this relationship was not found in healthy controls. In another study, [^{18}F]DOPA PET in patients with schizophrenia on antipsychotic medication revealed that

the dopamine synthesis capacity in the dorsal anterior cingulate was correlated with performance on the Stroop Color-Word Test (49).

During the manifestation of prodromal symptoms of schizophrenia before the onset of psychosis, patients showed elevated striatal dopamine synthesis capacity in the associative striatum (43). In that study, the at-risk mental state group showed a negative correlation between the dopamine synthesis capacity in the associative striatum and the performance on the semantic verbal fluency task, i.e., greater elevation in synthesis was associated with fewer correct responses and a similar negative correlation was observed for phonologic verbal fluency.

SEROTONIN (5-HYDROXYTRYPTAMINE, 5-HT)

In the human brain, the serotonergic system has 14 diverse receptor subtypes and transporters (50). Because of the availability of suitable radiotracers, extensive PET studies have been performed to investigate the availability of 5-HT1A and 5-HT2A receptors and the 5-HT transporter in various neuropsychiatric disorders. These receptors and transporters are of interest because they are main targets of pharmacotherapy via psychotropic drugs (51, 52). However, the number of imaging studies investigating the central serotonergic system in schizophrenia is limited (53).

5-HT1A Receptors

5-HT1A receptors are widely distributed in the hippocampal regions, insula, neocortical regions, and dorsal raphe nucleus (54). In addition, because the 5-HT1A receptor modulates the entire serotonin system, it is one of the most important 5-HT receptor subtypes (55). Several lines of evidence from animal studies and pharmacological studies indicate that the 5-HT1A receptor plays an important role in cognitive function and is a promising target for the treatment of cognitive and affective symptoms in neuropsychiatric disorders, including schizophrenia (51, 52, 55).

Thus far, four studies have examined 5-HT1A availability in schizophrenia, using the same PET tracer [^{11}C]WAY100635. One study reported an increase in 5-HT1A availability in the medial temporal cortex of schizophrenia patients (56), whereas another reported a decrease in the amygdala (57); the remaining two reported no difference in 5-HT1A availability between schizophrenia patients and healthy controls, although a meta-analysis of postmortem studies found an elevation in prefrontal 5-HT1A in schizophrenia (53).

With regard to cognitive function in healthy subjects, Yasuno et al. found a negative correlation between explicit memory function and 5-HT1A receptor availability in the hippocampus (58), while Borg et al., who performed [^{11}C]WAY100635 PET and used the same simplified reference model, found no correlation between regional 5-HT1A receptor availability in the raphe nuclei, hippocampus, and neocortex and various domains of cognitive performance (55, 59). However, a recent study by Penttila et al. found that global 5-HT1A receptor binding, measured with the gold standard method based on kinetic modeling using arterial blood samples, was positively correlated with measures of verbal memory in healthy subjects (60). To date, no 5-HT1A PET data have been reported for patients with schizophrenia in relation to cognitive function.

5-HT2A Receptor

A large body of evidence from postmortem and pharmacological studies suggests that 5-HT2A receptors play an important role in schizophrenia and cognition (51, 52). A meta-analysis of postmortem studies found a reduction in prefrontal 5-HT2A receptors in patients with schizophrenia (53). However, only a few PET studies have been performed on first-episode antipsychotic-naïve patients with schizophrenia, and their results are inconsistent (53). In a recent study with the largest sample size to date, a total of 30 patients with schizophrenia and matched healthy controls underwent [^{18}F]altanserin PET scans, which are highly selective for 5-HT2A receptors (61). Patients with schizophrenia showed lower 5-HT2A availability in the frontal cortex than healthy controls did. However, no correlations were found between 5-HT2A availability and cognitive functions such as working memory, attention, and executive functions, suggesting that 5-HT2A receptors are not involved in cognitive dysfunction, at least in the early stage of schizophrenia.

Serotonin Transporter (5-HTT)

A previous PET study with the 5-HTT-selective tracer [^{11}C]DASB found no significant difference in 5-HTT availability between patients with schizophrenia and healthy control subjects, and no correlation between 5-HTT availability and schizophrenia symptoms (62). In contrast, another [^{11}C]DASB PET study with healthy subjects found that 5-HTT availability in the fronto-striatal regions was associated with better performance on executive function and logical reasoning (63). To date, however, no PET studies have investigated the association between 5-HTT availability and cognitive function in patients with schizophrenia.

Other Serotonergic System

PET probes for 5-HT1B, 5HT4, 5-HT6, and 5-HT synthesis have been successfully used for human brain imaging (50); however, to date, no clinical studies have used these probes for imaging of the brains of patients with schizophrenia.

NOREPINEPHRINE

The central norepinephrine system plays crucial roles in arousal and concentration, and the norepinephrine transporter is a target in pharmacotherapy for depression and attention-deficit hyperactivity disorder. Despite this, few PET probes have been developed for norepinephrine transporter (NET) imaging (64). To date, there have been no reports of PET imaging of the NET in patients with schizophrenia.

DISCUSSION AND FUTURE DIRECTIONS

PET provides a direct way of investigating the neurotransmission and neurobiology of schizophrenia. Numerous PET studies have revealed differences between the brains of patients with schizophrenia and those of healthy controls, and the association of these brain changes with symptom scales, suggesting the underpinnings of the pathophysiology of this disorder. As reviewed above, however, only a limited number of PET studies have directly investigated the relationship between cognitive dysfunctions, assessed using neuropsychological tests, and monoamine transmission *in vivo*, and found significant associations between them. Consequently, dysregulated striatal dopamine synthesis capacity, and prefrontal D1 receptor and extrastriatal D2/D3 receptor availability might be at least partly indicative of cognitive impairment in schizophrenia. However, studies are scarce and not systematic: differences in radiotracers used, methods of quantification, neurocognitive tests employed, and patient characteristics (such as phase of the illness, prior exposure to antipsychotics, age, and sex) could be confounders. This scarcity and lack of systematic approaches occurs largely because it is difficult to recruit many patients with unmedicated schizophrenia; therefore, multi-site studies with common protocols are needed. Moreover, different approaches such as measuring endogenous release of transmitters rather than focusing only on baseline receptor availability, could be useful for precise evaluation of neurotransmission (65, 66). In summary, pharmacological challenge techniques such as that with amphetamine and dopamine depletion using [^{11}C]raclopride, which reflect presynaptic dopamine function, have been well replicated to detect dysregulated dopamine neurotransmission as a pathophysiology of schizophrenia (14, 67). Another approach is to measure changes in receptor binding of a radiotracer while performing a cognitive task as it accurately reflects the amount of neurotransmitter released during the task (68–70). Furthermore using agonist tracers such as [^{11}C]-(+)-PHNO and [^{11}C]MNPA, that can be more sensitive to endogenous transmitters, might help detect high affinity states of dopamine D2 receptors that could be more responsible for the pathophysiology based on a hypothesis from *in vitro* studies (71). Although studies on 5-HT1A receptors and 5-HT2A receptors have not demonstrated their involvement in cognition in schizophrenia, newer serotonergic targets, such as 5-HT4, might potentially be associated with cognitive functions (50). Regarding the norepinephrine system, one study reported a relationship between attention function and NET availability in patients with depression (72), which might be applicable to some patients with schizophrenia. Moreover, other neurotransmitter systems such as glutaminergic or cholinergic systems might also be involved in cognitive impairment in schizophrenia. Further development of optimal PET tracers and new techniques to measure more precise neurotransmission in human PET imaging will also provide new insights to the neurobiology of cognitive dysfunction in schizophrenia.

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Electrophysiological Evidence in Schizophrenia in Relation to Treatment Response

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Several domains of cognitive function, e.g., verbal memory, information processing, fluency, attention, and executive function are impaired in patients with schizophrenia. Cognitive impairments in schizophrenia have attracted interests as a treatment target, because they are considered to greatly affect functional outcome. Electrophysiological markers, including electroencephalogram (EEG), particularly, event-related potentials, have contributed to psychiatric research and clinical practice. In this review, we provide a summary of studies relating electrophysiological findings to cognitive performance in schizophrenia. Electrophysiological indices may provide an objective marker of cognitive processes, contributing to the development of effective interventions to improve cognitive and social outcomes. Further efforts to understand biological mechanisms of cognitive disturbances, and develop effective therapeutics are warranted.

Keywords: electroencephalogram, event related potentials, LORETA, cognition, schizophrenia

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INTRODUCTION

Cognitive impairments are considered as a fundamental feature of schizophrenia (1). Patients with the illness present disturbances across several cognitive domains, such as executive function, some types of memory, attention, fluency, and information processing/speed (2, 3). Cognitive function predicts social function more accurately than psychotic symptoms, and has been drawing attention as target of treatment (4, 5).

The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) (6) and the Brief Assessment of Cognition in Schizophrenia (BACS) (7) have been developed to evaluate disturbances of cognitive function in schizophrenia. Also, as an interview-based multidimensional assessment tool of social function, the Specific Level of Functioning Scale (SLOF) has been implemented (8). In fact, social functioning, as measured by the SLOF, has been shown to be correlated with cognitive function, as measured by the BACS in patients with schizophrenia (9).

There is evidence for the role of electrophysiological measures as an objective marker of neuropsychological performance (10–13). In fact, electrophysiological responses generally precede behavior-based cognitive performances, and are also useful to predict treatment outcome regarding cognitive disturbances (10, 14, 15). This paper provides selective reviews of studies on the relationships among cognitive function, electrophysiological findings, and treatment response in patients with schizophrenia.

ELECTROPHYSIOLOGICAL EVIDENCE IN SCHIZOPHRENIA

Spontaneous Electroencephalogram (EEG)

In general, functional neuroimaging techniques measuring blood flow and metabolism, such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and Single photon emission computed tomography (SPECT) may not directly differentiate between activation and inhibition of a specific brain region (16). On the other hand, EEG consists of components of electrical activities that are inhibitory (e.g., slow "delta" frequencies), excitatory (e.g., fast "beta" frequencies) or steady-state (mid-range "theta" and "alpha" frequencies) in nature (16). Also, EEG has an advantage in terms of time resolution compared to other techniques to evaluate brain functions.

Imaging of electrophysiological activity, such as EEG, is feasible and cost-effective. For example, Pascual-Marqui et al. developed the low-resolution brain electromagnetic tomography (LORETA) (16), which is a source localization analytic estimator. The purpose of current source localization is to overcome the volume conductance problem in EEG analyses and cope with the reference confounding effects (16). Neuroleptic-naïve patients with first-episode schizophrenia have been reported to demonstrate hyperactivity of delta band in the frontal-prefrontal area and hypoactivity of middle range band (theta and alpha) in the left temporal parietal area by means of LORETA (16). These findings support the concept that cognitive disturbances of schizophrenia are generated by inhibition of frontal and left temporal areas (17).

Functional deviations of frontal lobes are reflected by disturbances of executive function and working memory in schizophrenia (18, 19). In fact, a meta-analysis of studies using fMRI and PET reports reduced activation in dorsolateral prefrontal cortex and anterior cingulate cortex during executive functioning task performance in patients with schizophrenia (18). The dysfunction related to auditory verbal hallucinations (20) is consistent with the role for the left temporal lobe in auditory perception and language processing (21, 22).

Inhibited activities of the left temporal area in schizophrenia are also demonstrated by using PET (23). Further, dysfunction of fronto-temporal connectivity has been reported in schizophrenia (24), consistent with Fletcher et al. suggesting the role for this anatomical complex in the psychopathology of schizophrenia (17). Accordingly, an fMRI study reported the relation of fronto-temporal connectivity with cognitive functions, including working memory (25). The reduction of blood flow and metabolism in the frontal and left temporal areas in schizophrenia was supported by Pascual-Marqui et al. (16) who found inhibition of electrical activities in these brain regions.

On the other hand, there is a report that mid-fast band frequencies were not altered in medicated-free patients with schizophrenia (26), although delta band activities were increased. In this line, an increase in the delta activity was noted in frontal areas, left inferior temporal gyrus, and parahippocampal gyrus of neuroleptic-naïve patients with schizophrenia, as revealed by LORETA (27).

Event-Related Potentials

Event-related potentials (ERPs) are linked in time with physical and mental events, and are typically extracted from the scalp-recorded EEG by means of signal averaging (28). ERP components, such as P50, mismatch negativity (MMN), and P300, provide neural activities associated with sensory-perceptual and cognitive events in the order of milli-seconds (29). P50 and MMN reflects attention-independent (pre-attentive) automatic information processes, while P300 has been used as a measure of attentive information processes (30).

P50 is a pre-attentional component recorded about 50 ms after the presentation of an auditory stimulus in the conditioning-testing paradigm. Its amplitude is suppressed when a second click sound is presented 500 ms after an initial click (31). The P50 suppression is thought to reflect a sensory gating mechanism aimed at protecting against information overload (32). A meta-analysis study has reported robust P50 suppression deficits in schizophrenia (33). Specifically, deficits of P50 suppression have been linked to poor performance on tests of cognitive domains, such as attention (34–36), working memory (11, 36), processing speed (11, 34), and executive function (35). These associations suggest that impaired P50 sensory gating provides a targets of interventions to alleviate cognitive disturbances of schizophrenia (11).

MMN is typically recorded in the condition where a subject is instructed to divert attention from stimuli generated by the auditory oddball task (37). MMN is generated when a stimulus violates the invariance or regularity of the recent auditory past. For example, MMN is recorded when an deviant stimulus that differs in frequency, duration, intensity, or location is presented among repeatedly presented standard stimuli (38). MMN is considered to provide an index of (1) auditory sensory or echoic memory, and (2) context-dependent information processing at the level of the primary and secondary auditory cortices (38). Parameters of MMN, e.g., amplitudes and latencies, are thought to reflect the first step in a chain of events leading to the conscious detection of differences between auditory stimuli and variance in the auditory environment (38).

Reduction of MMN amplitudes in patients with schizophrenia shows a large effect size as demonstrated by meta-analysis (38). Specifically, patients with chronic schizophrenia show a decrease in MMN current density in the right medial frontal gyrus, right cingulate gyrus, and right paracentral lobule (39). Altered MMN amplitudes have been associated with impairment of cognitive functions, such as attention (12, 40, 41), processing speed (41, 42), verbal learning (40, 43), verbal fluency (44), and executive function (42). Also, its amplitudes have been linked to functional outcomes (45–47). Overall, pre-attentive information processes serve as a gateway to higher cognitive and psychosocial functioning (12). Further, the ability of MMN to reflect functional outcomes have been reported to be better than those of behavior-based cognitive performances and social cognition (15). These considerations further support the utility of MMN as a marker of treatment effects on social functioning.

P300 is typically recorded when a subject is required to pay attention to infrequent stimuli in an auditory oddball task (48). Amplitudes of P300 waveforms, thought to reflect cognitive processes such as directed attention and the contextual updating of working memory (31), are reduced, and the latency of P300 are delayed in patient with schizophrenia (33). Altered P300 activities have been reported to correlate with clinical symptoms of schizophrenia (37). By means of LORETA, current sources of P300 were estimated to reside in the bilateral medial frontal and medial parietal cortex, bilateral superior temporal gyrus, right temporo-parietal junction, and left lateral prefrontal cortex (37).

P300 amplitudes have been shown to positively correlate with performance on tests of verbal learning (49), organization and discriminability of memory (13), attention (50), verbal fluency (49), and executive function (49). Also, prolonged latency of P300 has been associated with performance on tests of verbal learning (13) and verbal fluency (51). It is important that these domains of cognition are related with functional capacity and real-world functions (9, 52). Further, a correlation has been reported between P300 amplitudes and functional capacity (53). These considerations support the potential utility of P300 as a biomarker to predict treatment response (53).

ELECTROPHYSIOLOGICAL CHANGES DURING TREATMENT

Spontaneous EEG

Using above-mentioned electrophysiological markers, some studies have reported the effect of treatment on cognitive disturbances of schizophrenia. Repetitive transcranial magnetic stimulation produced the following changes in patients with schizophrenia (54); (1) an increase in delta band activities in bilateral anterior cingulate gyrus, (2) a decrease in beta-1 and beta-3 band in the middle temporal lobe ipsilateral to the site of stimulation, and (3) an increase in beta-2 band in the middle temporal and inferior parietal lobule on the right side. In the same study (54), brain metabolism using ^{18}FDG-PET was simultaneously measured. While the change of current density of beta bands activities was in accordance with the PET findings, that of delta band was not correlated with brain metabolism (54).

ERPs

Using traditional ERP methods, some authors have investigated the effect of atypical antipsychotic drugs on cognitive function in schizophrenia. As to P50 suppression, treatment with quetiapine of antipsychotic-naïve first-episode patients improved the sensory gating deficits (55). In addition, some atypical antipsychotics, such as clozapine (56, 57) and risperidone (58), showed efficacy for the recovery of P50 suppression.

In treatment studies for the deficits of MMN in schizophrenia, aripiprazole has been reported to increase MMN amplitudes (59). On the other hand, other atypical antipsychotic drugs, such as clozapine (60), risperidone (61), and olanzapine (62) have been shown not to affect MMN amplitudes. Further study on the ability of medication to alleviate altered MMN parameters in the illness is warranted.

In the P300 study, a controlled double-blind trial investigated the effect of clozapine or haloperidol on ERPs, including P300 and MMN, in chronic schizophrenia (60). Treatment with clozapine, but not haloperidol was associated with an increase in P300 amplitudes (60). In another study, clozapine similarly increased P300 amplitudes, and also enhanced performance on working memory tasks (63). On the other hand, the effect of olanzapine on P300 has not been consistent (62, 64–66). Perospirone did not significantly affect P300 in schizophrenia (67).

Using three dimensional images of current density of ERPs in the brain, we reported the ability of treatment with olanzapine for 6 months to enhance P300 current density in the left STG, yielding a distribution pattern of the current density similar to that in healthy control subjects (68). A later study confirmed treatment with olanzapine was associated with increase of P300 current source density in the left STG (69). Importantly, the degree of increase of P300 in the left STG was positively correlated with improvement in negative symptoms and verbal learning memory, while improvement of quality of life was associated with an increase of P300 in the left prefrontal cortex (69). On the other hand, treatment with perospirone was found to improve P300 current density in the left prefrontal cortex, which was related with improvement of daily-living skills, as measured by the script task (70). These findings suggest LORETA imaging of P300 is a useful indicator of treatment response in some aspects of the psychopathology and functional outcomes of schizophrenia.

CLINICAL IMPLICATIONS

Early intervention into schizophrenia and related conditions has been suggested to improve the prognosis of patients. Accordingly, shorter duration of untreated psychosis has been associated with better long term outcomes (71). Electrophysiological measures may be useful to evaluate the risk for developing psychosis. For example, P300 amplitudes are reduced in the prodromal stage (72, 73). Specifically, treatment with perospirone in an ultra-high risk case immediately before the onset of schizophrenia was shown to "normalize" cognitive function and social outcomes 3 years later. Importantly these neuropsychological and clinical events were preceded by improvement of P300 amplitudes (14). Also, MMN amplitudes have been shown to identify high-risk individuals who later develop overt schizophrenia (44, 74). Taken together, electrophysiological indices may provide a sensitive marker to evaluate treatment effects, including those related to cognitive function, and in some cases, predict the risk of psychosis.

CONCLUSIONS

In this review, we have provided a summary of studies relating electrophysiological findings to cognitive performance in schizophrenia. Electrophysiological indices may provide an objective marker of cognitive processes, contributing to the development of effective treatment of cognitive and social

outcomes. Further efforts to understand electrophysiological mechanisms of cognitive disturbances, and develop effective therapeutics are warranted.

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ORIGINAL RESEARCH
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Sensorimotor Gating in Depressed and Euthymic Patients with Bipolar Disorder: Analysis on Prepulse Inhibition of Acoustic Startle Response Stratified by Gender and State

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Background: Prepulse inhibition (PPI) of the acoustic startle reflex is an operational measure of sensorimotor gating. The findings on PPI deficits in bipolar disorder (BD) are inconsistent among studies due to various confounding factors such as gender. This study aimed to assess sensorimotor gating deficits in patients with BD stratified by gender and state (depressed/euthymic), and to explore related clinical variables.

Methods: Subjects were 106 non-manic BD patients (26 BD I and 80 BD II; 63 with depression and 43 euthymic) and 232 age-, gender-, and ethnicity-matched (Japanese) healthy controls. Depression severity was assessed using the Hamilton Depression Rating Scale-21. The electromyographic activity of the orbicularis oculi muscle was measured by a computerized startle reflex test unit. Startle magnitude, habituation, and PPI were compared among the three clinical groups: depressed BD, euthymic BD, and healthy controls. In a second analysis, patients were divided into four groups using the quartile PPI levels of controls of each gender, and a ratio of the low-PPI group (<1st quartile of controls) was compared. Effects of psychosis and medication status were examined by the Mann–Whitney *U* test. Clinical correlates such as medication dosage and depression severity with startle measurements were examined by Spearman's correlation.

Results: Male patients with depression, but not euthymic male patients, showed significantly lower PPI at a prepulse of 86 dB and 120 ms lead interval than did male controls. More than half of the male patients with depression showed low-PPI. In contrast, PPI in female patients did not differ from that in female controls in either the depressed or euthymic state. Female patients with active psychosis showed significantly lower PPI than those without psychosis. Female patients on typical antipsychotics had significantly lower PPI, than those without such medication. PPI showed a significant positive correlation with lamotrigine dosage in male patients and lithium dosage in female patients.

Conclusion: These findings suggest that sensorimotor gating is impaired in male BD patients with depression. However, we obtained no evidence for such abnormalities in female BD patients except for those with current psychosis. The observed associations between medication and startle measurements warrant further investigation.

Keywords: prepulse inhibition, bipolar disorder, habituation, depression, euthymic, gender difference, psychosis

INTRODUCTION

Prepulse inhibition (PPI), an operational measure of sensorimotor gating, is defined as the attenuation of the startle reflex when the startle-eliciting stimulus—the pulse—is preceded by a weaker sensory stimulus—the prepulse (PP) (1). It is typically measured by electromyographic (EMG) recordings from the orbicularis oculi muscle and is a very robust function; it is conserved across many species (2). PPI deficits have been associated with multiple neuropsychiatric disorders characterized by inhibitory deficits in sensory, motor, and cognitive functions, including schizophrenia, psychotic mania, obsessive–compulsive disorder, and Tourette syndrome (3, 4). Our group demonstrated PPI deficits in Asian individuals with schizophrenia for the first time (5), and subsequently reported that PPI was impaired in female and male patients with schizophrenia using a large sample of single ethnicity patients and healthy individuals (Japanese) (6). Brain imaging studies have revealed common abnormalities in the cortico–striato–pallido–pontine and cortico–striato–pallido–thalamic (CSPT) circuitries across these disorders; these circuits are considered to affect disease pathophysiology and PPI modulation (3, 7). Accumulating evidence from animal and human studies indicates that PPI is also modulated by top-down, higher-order cognitive regions, such as the hippocampus, medial prefrontal cortex (mPFC), orbitofrontal cortex (OFC), and basolateral amygdala (4, 8, 9). The amygdala, mPFC, and OFC, as well as the anterior cingulate gyrus and insula, have been consistently shown to be associated with emotional processing (10–12). These nuclei are dense in noradrenergic receptors and critical for the regulation of the hypothalamic–pituitary–adrenal and hypothalamic–pituitary–gonadal axes (13). Pharmacological studies in animal models of schizophrenia have also suggested the involvement of several neurotransmitter pathways, including dopaminergic, serotonergic, glutamatergic, and cholinergic pathways, in PPI deficiency (3, 14).

Prepulse inhibition deficits in patients with schizophrenia have been reported to be associated with positive symptoms (6, 15–18), negative symptoms (15, 18), disorganization symptoms (6), distractibility (19), thought disorder (20, 21), formal thought disorder and bizarre behavior (22), psychological discomfort (23), and general psychopathology (18, 24). A longitudinal study on patients with schizophrenia reported that PPI deficits in medicated patients were observed in acute illness, but not in an improved clinical state, which suggests that PPI deficits may be state dependent (22).

While PPI deficits in schizophrenia have been reported in many studies (3), little is known about gating differences in patients with BD (4), despite the occurrence of psychotic symptoms and cognitive impairments similar to schizophrenia patients (25, 26). Moreover, larger brain ventricle volumes and structural abnormalities in CSPT circuits have been detected in BD patients (27, 28). Genome-wide association studies (GWAS), human postmortem brain studies, and magnetic resonance spectroscopy studies have identified similar gene expression changes in glutamatergic neurotransmission and glutamate receptor (GluR) expression among patients with schizophrenia, BD, and major depressive disorder (MDD) (29–32). Since the glutamatergic *N*-methyl-D-aspartate receptors (NMDA) receptor antagonist, such as ketamine and phencyclidine, disrupt PPI (3), it is possible that the PPI may be impaired in BD. However, to our knowledge, there are only two studies that examined PPI in BD patients in manic states, and five studies in euthymic states, both with inconsistent findings. Perry et al. reported that PPI and habituation were exacerbated in acute psychotic mania, suggesting a possible association between PPI deficits, psychosis, and thought disturbance (33). A subsequent study by Carroll et al. failed to replicate these findings in manic and mixed episodic patients. Since almost all the patients in the latter study did not have psychosis (with only 1 exception), they concluded that acute psychosis might be necessary for the occurrence of BD-associated PPI deficits (34). In euthymic patients with BD, controversial results of both unimpaired (35, 36) and significantly lower PPI (37, 38) have been reported. Giakoumaki's study also found reduced PPI in unaffected siblings of BD patients, suggesting that such disruption may represent a trait deficit in BD. All the above studies were conducted with men and women included in the same group, although gender-related differences in PPI (men > women) have been well-replicated in healthy subjects (3, 39–42). It is known that women present fluctuations in PPI across the menstrual cycle, with the lowest PPI in the mid-luteal phase when ovarian hormones (estrogen and progesterone) are maximal (41, 43, 44). Thus, Gogos et al. examined PPI in euthymic patients with BD stratified by gender and reported sexually dimorphic differences: male patients showed reduced PPI, while female patients in the follicular phase had increased PPI compared to their healthy counterparts (45). No study has yet assessed the PPI in BD patients with depression and the association of PPI with depression severity. Thus, it is still unclear whether PPI deficits represent a state or trait feature of BD.

Prepulse inhibition in patients with MDD was generally considered unimpaired (46–48); however, Perry et al. (46) observed moderate effect size of difference (Cohen's $d = 0.63$) between patients with severe MDD and healthy controls. MRI examination of MDD patients revealed abnormalities in CSPT circuitry similar to those observed in patients with schizophrenia and BD (49–52), and two recent studies have found PPI deficits in MDD patients. One is ours reporting a significant negative correlation between PPI and depression severity in male, but not female, patients, suggesting that PPI impairment is state- rather than trait-dependence in male patients with MDD (53). The other

study found PPI deficits in women with postpartum depression compared to their non-depression counterparts, when effects of ovarian hormones were minimal in all subjects (54).

In addition to gender, there are other factors that may influence PPI, such as age (55–57), ethnicity (58), and smoking status (59–62). Ethnic differences in startle magnitude and PPI were reported between Caucasians and Asians, with Asians having lower startle magnitude and higher PPI compared to Caucasians (58, 63, 64). To control for these confounding factors, we matched for age, gender, smoking status, and ethnicity.

In this study, we examined the modulation of the startle reflex in non-manic BD patients with the following aims: (1) to investigate whether BD patients with depression show deficits in PPI, startle reactivity, and habituation compared to euthymic patients and healthy individuals, and (2) to examine whether such deficiencies, if any, are associated with symptoms and other clinical features. Data acquired from men and women were analyzed separately. Based on our previous findings of reduced PPI in male patients with MDD, we hypothesized that depressed patients with BD, especially men, may also present PPI deficits. Additionally, we hypothesized that PPI deficits, if any, may be associated with depression severity, the presence of current psychosis, and more severe psychopathology.

MATERIALS AND METHODS

Subjects

Subjects included 338 volunteers, consisting of 106 non-manic BD patients (26 BD I and 80 BD II; 63 patients with depression and 43 euthymic patients, see definition below) and 232 healthy individuals (age: 18–64 years). Data from control subjects were age-, gender-, and ethnicity-matched (Japanese) with those acquired from BD patients. Participants were recruited for neurocognitive research studies between 2009 and 2017 at the National Center of Neurology and Psychiatry (NCNP), Tokyo, Japan, through notices posted in the NCNP Hospital, website announcements, and advertisements in a local free paper. Most healthy individuals used as controls overlapped with those from our previous studies (6, 53). The participants were either NCNP Hospital inpatients (14%) or outpatients from the NCNP Hospital or other local hospitals and clinics.

All subjects were interviewed by experienced psychiatrists using the Japanese version of the Mini-International Neuropsychiatric Interview (65, 66). Diagnoses were further confirmed through medical records and detailed interviews based on the Diagnostic and Statistical Manual (DSM) of Mental Disorders, Fourth Edition, text revision (DSM-IV-TR) (67). Individuals with a concurrent confirmed diagnosis of intellectual disability or organic brain disorder, ongoing thyroid gland malfunction, undergoing electroconvulsive therapy treatment or substance abuse history in the previous year were excluded from this study. Patients with concurrent psychiatric disorders, such as anxiety disorder, panic disorder, autism spectrum disorder (ASD), or attention-deficit hyperactivity disorder, were included in this study. Control subjects with a psychiatric history or family history of mental illness within second-degree relatives (schizophrenia, BD, and ASD) were excluded from this study. None of the subjects presented with hearing deficits as confirmed by audiometry (threshold: average hearing level of 500, 1,000, and 2,000 Hz to <40 dB). Premorbid intelligence quotient (IQ) was estimated from the Japanese Adult Reading Test scores (68) and only individuals with premorbid IQ $\geq$ 85 were included in this study.

The depression severity of subjects with BD was assessed using the 21-item version of the Hamilton Depression Rating Scale (HAM-D21) (69). Manic symptoms of subjects with BD were assessed by the Young Mania Rating Scale (YMRS) (70). Based on the definition of manic states, as determined by the International Society for Bipolar Disorders Task Force (71), those in a significant manic, hypomanic, or mixed state (i.e., YMRS score $\geq$ 8) were excluded. Subjects with BD were further categorized into either the depressed (HAM-D17 $\geq$ 8 and YMRS < 8) or euthymic (HAM-D17 < 8 and YMRS < 8) group, according to the consensus definition for remission (72). A daily dose of antidepressants was calculated as imipramine equivalents, and antipsychotics as chlorpromazine equivalents in milligrams/day according to the published guidelines (73).

This study was conducted following the latest version of the Declaration of Helsinki. The study design was reviewed and approved by the NCNP Ethics Committee. Written informed consent for participation in this study was obtained from every subject after the nature of the procedures had been fully explained.

Startle Reflex Measurement

PPI Paradigm

The EMG activity of the orbicularis oculi muscle was measured by a computerized startle reflex test unit. All participants were requested to refrain from smoking at least 30 min prior to testing, based on a previous study reporting that the PPI-enhancing effect of smoking lasts only for a short period (less than 10 min) (61). The apparatus, procedures, stimuli, and PPI paradigm used have been described in detail elsewhere (5, 53). Briefly, each session consisted of three blocks with 70 dB background noise. Blocks 1 and 3 consisted of additional 115 dB pulse alone (PA; five times each) trials. Block 2 was a pseudo-randomized combination of the same PA together with PP trials under four conditions (lead interval, intensity: 60 ms, 86 dB; 60 ms, 90 dB; 120 ms, 86 dB; 120 ms, 90 dB; five times each). In total, 35 trials of startle reflex were carried out in one session, lasting for 15 min.

Outcome Measures and Data Reduction

Outcome measures for analysis were as follows: (1) mean PA startle reflex magnitude (digital unit) in block 1, defined as basic startle reflex (BSR), (2) startle reflex habituation (%), and (3) PPI (%) for each PP condition. Mean PPI calculation and habituation were performed as described elsewhere (5, 53). Non-responding subjects were excluded from any further analysis ($n = 45$; BSR < 0.05 digital unit). Therefore, viable habituation and PPI data were collected from 87 BD patients and 206 healthy controls (total $n = 293$).

Statistical Analysis

Statistical analyses were performed using SPSS Version 22.0 (SPSS Japan, Tokyo). Groups were compared based on demographic and clinical characteristics using independent Student's

t-tests or one-way analysis of variance for continuous variables and chi-squared test for categorical variables. Data from the left eye were selected for analysis because no sidedness was detected in any startle reflex measurements. According to the Shapiro–Wilk test, data from all startle measurements were not normally distributed (all $p < 0.001$); therefore, non-parametrical analyses were applied to these variables. We compared the startle measurements of three clinical groups (i.e., depressed BD, euthymic BD, and healthy control) with the Kruskal–Wallis test, followed by between-group comparisons with the Mann–Whitney *U* test. The findings were confirmed when patients with concurrent psychiatric disorders, such as anxiety disorder, panic disorder, ASD, and/or attention-deficit hyperactivity disorder, were excluded; therefore, they were retained in the analysis. Subjects were further subcategorized into four groups using the quartile PPI_{120ms_86dB} levels of controls for each gender. Then, the incidence of the low-PPI (first quartile group) vs. high-PPI (second to fourth quartile groups) was compared between patients and controls by the chi-squared test and across the three clinical groups by the Fisher's exact test. Effects of active psychosis and medication status on habituation and PPI were examined by the Mann–Whitney *U* test. Spearman's rank correlation coefficients of habituation and PPI percentage with clinical variables were computed. Statistical significance was set at a two-tailed $p < 0.05$.

RESULTS

Demographic and clinical characteristics of the total subjects are presented in **Table 1**. Because of the *a priori* matching, the two diagnostic groups were similar concerning gender and age distribution. Education years, current smoker ratio, and estimated premorbid IQ were not significantly different between the diagnostic groups. However, when non-responders were excluded, age and premorbid IQ were significantly higher in male controls than male patients [$t(77.1) = 2.018$, $p = 0.047$ and $t(104) = 2.068$, $p = 0.041$, respectively] (Table S1 in Supplementary Material). Depression severity in responders was not significantly different between male and female patients either in the total [$t(56.2) = 0.667$, $p = 0.508$], depressed [$t(53) = 1.560$, $p = 0.125$] or euthymic group [$t(30) = -0.543$, $p = 0.591$]. Comparisons of startle reflex responses between the diagnostic groups and across the three clinical groups are shown in **Figures 1** and **2**, respectively, as well as in Table S2 in Supplementary Material. The same comparison was made excluding patients with concurrent psychiatric disorders, and the results are provided in Table S3 in Supplementary Material. The ratio of the number of individuals in the PPI quartile groups of depressed and euthymic patients is shown in **Figure 3**. Effects of active psychosis and medication status, and correlation of clinical variables with habituation and PPI are presented in **Tables 2** and **3**, respectively.

Startle Reflex and Habituation

Neither BSR magnitude nor habituation percentage significantly differed between the two diagnostic groups or among the three clinical groups. Neither BSR nor habituation correlated with the total HAM-D21 or YMRS, respectively. BSR negatively correlated with age in male patients ($\rho = -0.481$, $p = 0.001$), but significance disappeared when non-responders were excluded ($\rho = -0.270$, $p = 0.129$). Female patients medicated with sodium valproate and/or atypical antipsychotics exhibited significantly lower habituation than did those without such medication. Habituation in female patients was significantly negatively correlated with lithium dosage ($\rho = -0.570$, $p = 0.033$). No other association with habituation was found.

Prepulse Inhibition

Comparisons Between Clinical Groups

Male patients showed significantly lower PPI than male controls at PPI_{120ms_86dB} ($U = 913.0$, $p = 0.034$); however, female patients did not show a significant difference from female controls at any PP condition. Stratified analysis across the three clinical groups detected significantly reduced PPI in depressed male patients compared to male controls at PPI_{120ms_86dB} [$\chi^2(2) = 6.456$, $p = 0.040$], while there were no statistically significant differences between euthymic male patients and male controls or between euthymic and depressed male patients. PPI in female patients did not differ from that in female controls either in the depressed or the euthymic state. The results were virtually the same when we excluded patients with concurrent psychiatric disorders (Table S3 in Supplementary Material). When we examined the incidence of low-PPI (first quartile of controls) vs. high-PPI (second to fourth quartiles) across the three clinical groups, there was a significantly higher incidence of low-PPI among male patients with depression (55%) compared to their respective controls ($p = 0.039$; **Figure 3**; Table S2 in Supplementary Material). There was also a trend for a higher incidence of low-PPI in male patients with depression compared to euthymic male patients ($p = 0.070$).

Effects of Active Psychosis and Medication Status on PPI

Female patients with active psychosis showed significantly lower PPI than did those without psychosis. Female patients on typical antipsychotics had significantly lower PPI than those without such medication (**Table 2**).

Correlation of Clinical Variables With PPI

There was a trend for HAM-D21 total to correlate negatively with PPI in male ($\rho = -0.309$, $p = 0.086$ at PPI_{120ms_86dB}) and female patients ($\rho = -0.253$, $p = 0.065$ at PPI_{120ms_90dB}). YMRS score was not correlated with PPI. PPI was significantly positively correlated with lamotrigine dosage in male patients ($\rho = 0.813$, $p = 0.002$ at PPI_{120ms_90dB}), and lithium dosage in female patients ($\rho = 0.691$, $p = 0.006$ at PPI_{120ms_86dB}) (**Table 3**). No other association with PPI was found.

DISCUSSION

To our knowledge, this is the largest PPI study in BD patients ($n = 106$), and the first study exploring PPI in BD patients with depression ($n = 63$). The large sample size enabled us to conduct the analyses stratified by gender and state (depressed/euthymic). This study aimed to clarify how a state (i.e., depressed/euthymic) is associated with PPI in non-manic BD patients. Our main

TABLE 1 | Demographic and clinical data of the subjects stratified by gender (mean ± SD).

	Bipolar disorder			Healthy controls			Statistical comparison		
	Total	**Men**	**Women**	**Total**	**Men**	**Women**	**Total**	**Men**	**Women**
Gender ratio, *N* (%)[a]	106	44 (42%)	62 (58%)	232	93 (40%)	139 (60%)	x^2(l) = 0.061, p = 0.805	–	–
Age (years)	39.3 ± 10.0	40.5 ± 9.9	38.4 ± 10.2	41.6 ± 12.2	43.0 ± 13.1	40.7 ± 11.6	t(244.4) = 1.863, p = 0.064	t(109.1) = 1.232, p = 0.220	t(199) = 1.362, p = 0.175
Education (years)	15.1 ± 2.4	15.3 ± 2.1	14.6 ± 2.0	14.9 ± 2.1	15.7 ± 2.8	14.6 ± 2.1	t(336) = −0.739, p = 0.460	t(135) = −1.056, p = 0.293	t(199) = 0.018, p = 0.985
Current smoker, *N* (%)[a,b]	23 (22%)	14 (33%)	9 (15%)	46 (20%)	24 (26%)	22 (16%)	x^2(l) = 0.179, p = 0.672	x^2(l) = 0.550, p = 0.458	x^2(l) = 0.045, p = 0.831
Premorbid IQ[c]	112 ± 9	112 ± 9	112 ± 8	113 ± 7	114 ± 7	112 ± 7	t(330) = 0.530, p = 0.597	t(131) = 1.708, p = 0.090	t(197) = −0.764, p = 0.446
Range	85–126	88–125	85–126	92–127	92–127	93–124			
Clinical variables	**Total**	**Men**	**Women**	**Men vs. women**					
Bipolar LN (%)[a]	26 (25%)	9(21%)	17(27%)	x^2(l) = 0.674, p = 0412					
Inpatients, *N* (%)[a,d]	14(14%)	6(14%)	8(14%)	x^2(l) = 0.001, p = 0.972					
Age of onset (years)	29.2 ± 9.9	30.8 ± 10.0	28.0 ± 9.7	t(104) = 1.432, p = 0.155					
Duration of illness (years)	11.5 ± 8.1	11.2 ± 8.3	11.8 ± 8.1	t(104) = −0.369, p = 713					
History of hospitalization, *N* (%)[a,e]	41 (40%)	18 (41%)	23 (40%)	x^2(l) = 0.016, p = 0.898					
Number of hospitalization[e]	0.95 ± 1.6	0.95 ± 1.5	0.95 ± 1.7	t(100) = 0.019, p = 0.985					
Medication use									
Lithium use, *N* (%)[a]	39 (37%)	23 (52%)	16(26%)	x^2(l) = 7.752, $\mathbf{p = 0.005}$					
Valproic acid use, *N* (%)[a]	25 (24%)	8 (18%)	17 (27%)	x^2(l) = 1.219, p = 0.270					
Lamotrigine use, *N* (%)[a]	21 (20%)	13 (30%)	8 (13%)	x^2(l) = 4.487, $\mathbf{p = 0.034}$					
Antidepressant use, *N* (%)[a]	48 (45%)	24 (55%)	24 (39%)	x^2(l) = 2.605, p = 0.107					
Typical antipsychotics use, *N* (%)[a]	14(13%)	4 (9%)	10(16%)	x^2(l) = 1.112, p = 0.292					
Atypical antipsychotics use, *N* (%)[a]	42 (40%)	23 (52%)	19 (31%)	x^2(l) = 5.032, $\mathbf{p = 0.025}$					
Anxiolytics/hypnotics use, *N* (%)[a]	67 (63%)	31 (71%)	36 (58%)	x^2(l) = 1.699, p = 0.192					
Medication dosage (if any; mg/day)									
Lithium	587 ± 276	552 ± 292	638 ± 253	t(37) = −0.947, p = 0.350					
Sodium valproate	476 ± 260	450 ± 302	488 ± 247	t(23) = −0.336, p = 0.740					
Lamotrigine	157 ± 62	156 ± 72	159 ± 48	t(19) = −0.126, p = 0.901					
Antidepressant[f]	181 ± 138	192 ± 158	169 ± 116	t(45) = 0.579, p = 0.565					
Typical antipsychotics[g]	24 ± 22	35 ± 36	20 ± 16	t(10) = 1.047, p = 0320					
Atypical antipsychotics[g]	179 ± 319	283 ± 276	273 ± 367	t(42) = 0.095, p = 0.925					
Symptoms									
HAM-D21 total score	12.0 ± 8.4	12.2 ± 9.1	11.8 ± 8.0	t(104) = 0.242, p = 0.809					
YMRS total score[h]	1.7 ± 1.8	2.0 ± 1.7	1.5 ± 1.8	t(63) = 1.204, p = 0.233					

[a]*Chi-square test was conducted.*

[b]*Information on current smoking status was missing in two (2%) patients and three (1%) controls.*

[c]*Premorbid intelligence quotient (IQ) was estimated from the Japanese Adult Reading Test, which was administered on 100 (94%) subjects with bipolar disorder and all the control subjects.*

[d]*Information was missing in seven (7%) patients.*

[e]*Information on the history of hospitalization was missing in four (4%) patients.*

[f]*Imipramine equivalent for those who received antidepressant medication.*

[g]*Chlorpromazine equivalent for those who received antipsychotic medication.*

[h]*Young Mania Rating Scale (YMRS) data for 19 (43%) male and 22 (35%) female patients were missing.*

Statistical significance was set at a two-tailed $p < 0.05$. Bold figures represent significant p value.

HAM-D21, 21-item version of the Hamilton Depression Rating Scale; YMRS, Young Mania Rating Scale.

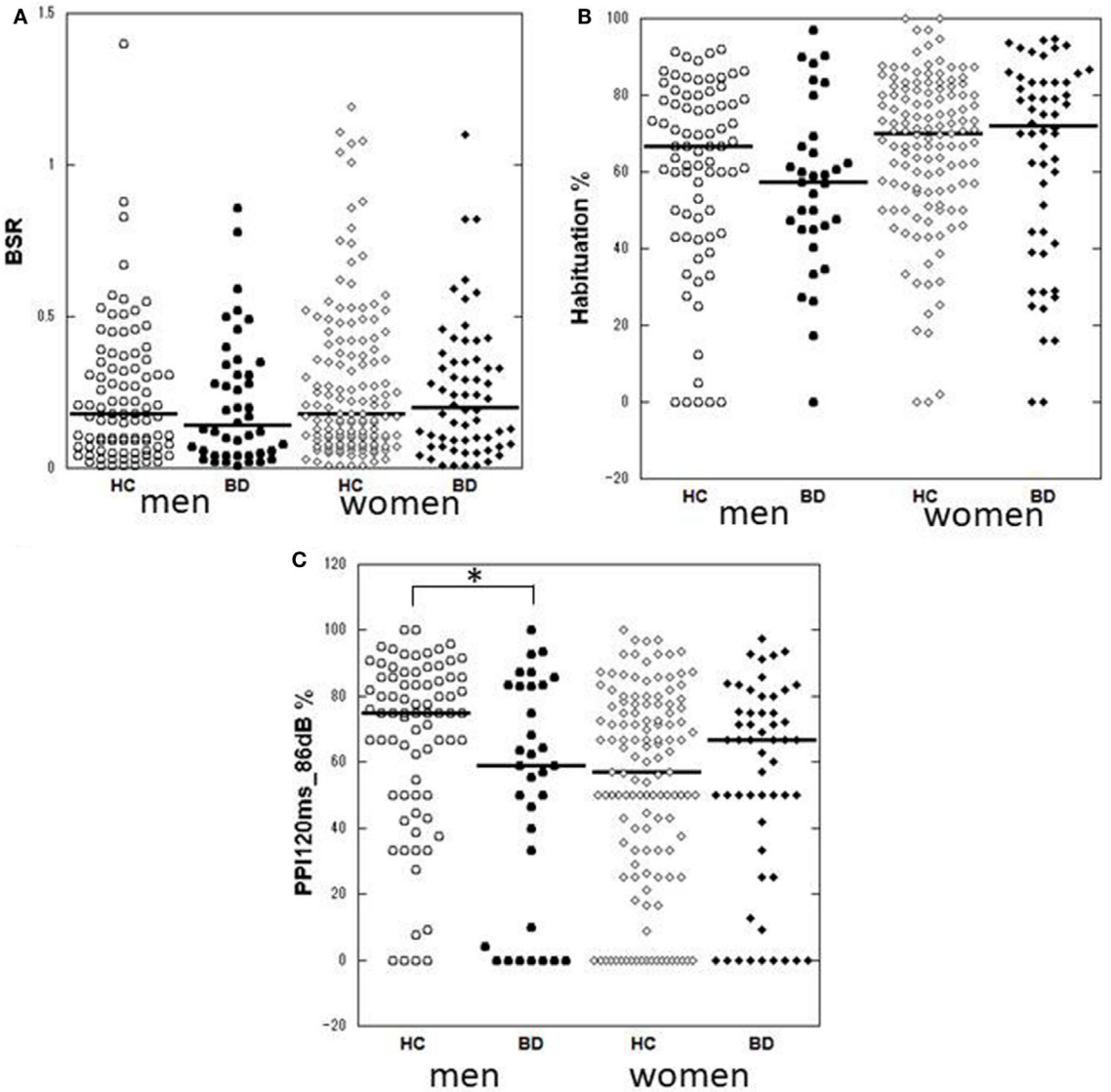

FIGURE 1 | Dot-plots of startle measurements of the two diagnostic groups by gender. **(A)** Basic startle reflex (BSR) in block 1. **(B)** Habituation percentage. **(C)** Prepulse inhibition (PPI) percentage at a prepulse of 120 ms at 86 dB. Bar indicates median. Habituation and PPI < 0% are shown as 0%. Between-group differences were examined by the Mann–Whitney *U* test. *$p < 0.05$ uncorrected. HC, healthy control; BD, bipolar disorder.

findings are as follows. First, as hypothesized, male patients with BD, but not female patients, had significantly lower PPI than male controls at one of the PP conditions (PPI_{120ms_86dB}). More specifically, male patients with depression, but not euthymic male patients, had significantly lower PPI than male controls. More than half of the male patients with depression had low-PPI (< first quartile of male controls). In contrast, PPI in female patients did not differ from that in female controls, either in the depressed or the euthymic state. Female patients with active psychosis showed significantly lower PPI than those without psychosis. Female patients on typical antipsychotics had significantly lower PPI than those without such medication. PPI was significantly positively correlated with lamotrigine dosage in male patients and lithium dosage in female patients.

Few studies have investigated PPI in psychiatric disorders separately by gender and most reported that PPI deficits were found only in male patients, such as those with chronic schizophrenia (74), euthymic BD (45), and MDD (53). The present finding is in line with those studies but it contradicts with our previous study which found PPI deficits both in men and women with schizophrenia (6). The seemingly intact PPI in female BD in the present study is in line with the above report on euthymic BD by Gogos et al. (45), which tested female subjects who were all in the follicular phase and reported that PPI in female BD was significantly higher than that in female controls. Our study did not control the time of testing in the menstrual cycle; however, we have previously obtained similar results of seemingly intact PPI in female MDD and speculated that possible menstrual irregularity

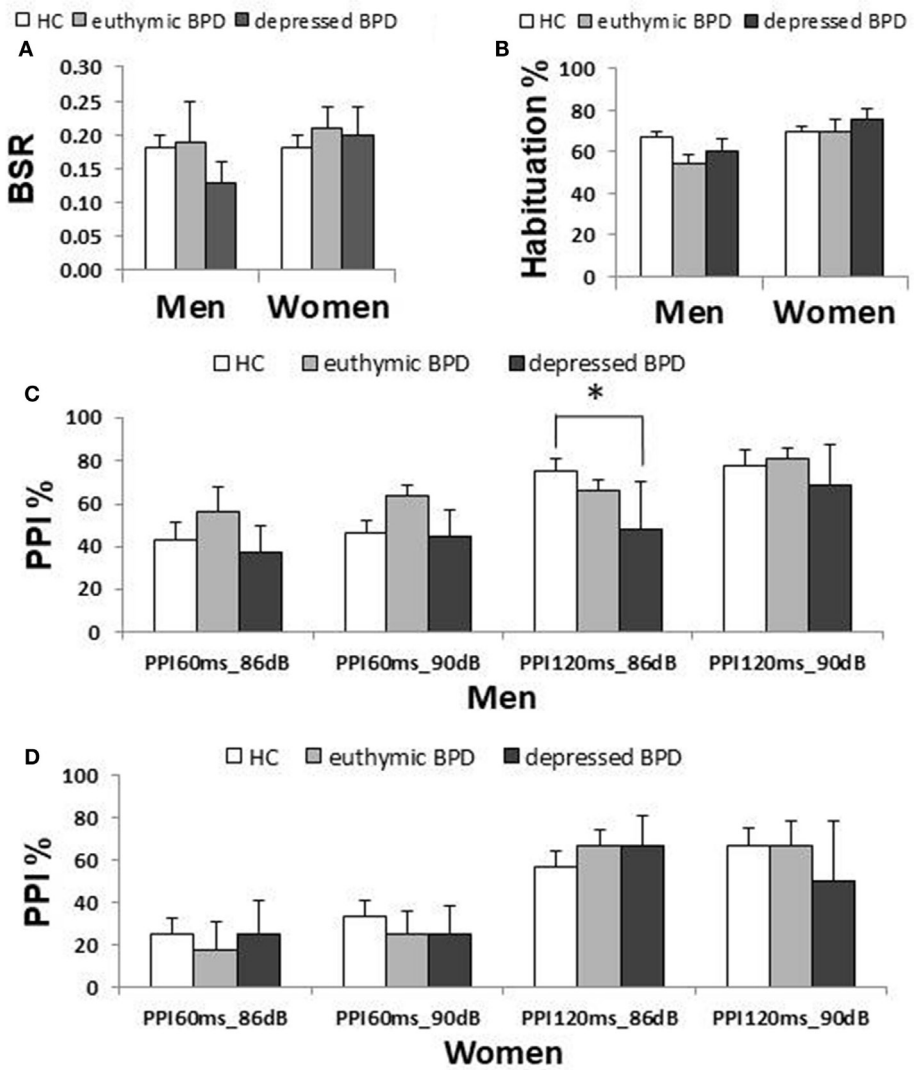

FIGURE 2 | Comparison of startle measurements across the three clinical groups by gender (median ± SEM). **(A)** Basic startle reflex (BSR) in block 1. **(B)** Habituation percentage. **(C)** Prepulse inhibition (PPI) percentage in different prepulse parameter trials in men. **(D)** PPI percentage in women. Bar indicates median. Error bar indicates SEM. Between-group differences were examined by the Mann–Whitney *U* test. *$p < 0.05$ corrected. HC, healthy control; BD, bipolar disorder.

in some female patients caused by psychotropic medication, insomnia, and psychological stress might have increased PPI in female patients (53). Future studies on women should be made in the follicular phase to minimize the effects of circulating ovarian hormones.

Our finding of impaired PPI in male BD patients with depression and seemingly intact PPI in euthymic males with BD suggests that PPI is state dependent in men with BD. We also found a trend for the HAM-D21 total to correlate negatively with PPI in male and female BD. However, since the number of euthymic male BD is limited ($n = 13$), the above finding may have the risk of type II error. Gogos et al. (45) reported the presence of PPI deficits in the euthymic male with BD; however, half of their male patients (10/18) had mild to severe depression and, therefore, may not be described as "euthymic" (45). Other studies which examined PPI in euthymic BD in an equal mix of men and women found inconsistent results: two studies found normal PPI (35, 36), whereas the other two studies reported significant PPI deficits in euthymic BD (37, 38). A possible reason for such inconsistency may be that the latter two studies tested only patients with BD I, whereas there were only two euthymic and six depressed patients with BD I among the responders in our study. We conducted a sensitivity analysis excluding male patients with BD I and found that the results were virtually unchanged (median PPI_{120ms_86dB} was 66% in 11 euthymic male patients and 48% in 14 depressed male patients). Again, we found significant differences between depressed BD II patients and controls ($U = 301.0$, $p = 0.009$) and between depressed BD II patients and euthymic BD II patients ($U = 36.0$, $p = 0.048$), but no significant difference between euthymic BD II patients and controls, in men. Taken together,

PPI in patients with BD II may be state dependent. To address this issue, further longitudinal studies are required.

Against our second hypothesis, we were unable to find a significant correlation between startle measurements (habituation and PPI) and variables related to the severity of psychopathology, such as the age of illness onset, duration of illness, and the number of hospitalization. Barret et al. found a significant correlation between PPI and these clinical variables, concluding that an early onset of illness has a detrimental effect on PPI levels (35). Gogos et al. also found a trend for a correlation between PPI and age of onset in male BD patients (45). Our finding that female BD patients with current psychosis had a significantly lower PPI than those without such psychosis is in line with the previous literature indicating the association of PPI deficits with the presence of psychosis and thought disorder (20, 33, 34). However, psychosis might not be a key determinant, considering that we were unable to find such an association in males.

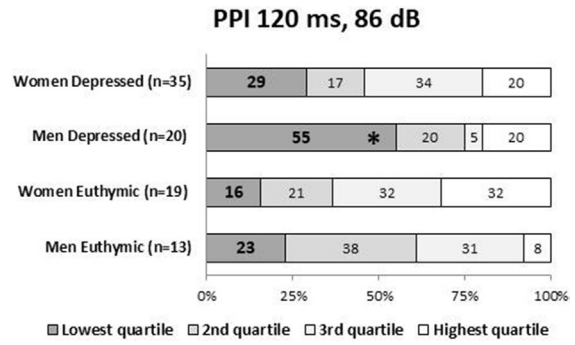

FIGURE 3 | Ratio (%) of the PPI quartile groups in depressed and euthymic patients by gender. Patients were categorized into four groups using the PPI quartiles of healthy men and women. The incidence of the low-PPI (lowest quartile group) vs. high-PPI (second to fourth quartile groups) was compared across the three clinical groups by the Fisher's exact test. Statistical significance was set at a two-tailed $p < 0.05$. *$p < 0.05$ against controls. PPI, prepulse inhibition.

Psychotropic medication may be a possible confounding factor that may have masked the direct association of depression with PPI. In the present study, we obtained tentative evidence of deteriorating effects of sodium valproate and/or atypical antipsychotics on habituation and typical antipsychotics on PPI in female patients. Some studies suggest that atypical antipsychotics may improve PPI deficits in schizophrenia (64); however, we were unable to find such an effect in BD patients. The imbalance in monoaminergic neurotransmission, changes in the activity of monoamine transporters, hyper- and hypo-dopaminergic function, and imbalance of excitatory/inhibitory neurotransmission by glutamate and γ-aminobutyric acid (GAVA) systems have been posited as the neurobiological hypotheses of BD (30). In the present study, neither patients medicated with antipsychotics, antidepressants, nor mood stabilizers showed better PPI than those who were not medicated. On the other hand, we found a strong positive correlation of PPI with lamotrigine dosage in male and lithium in female patients. These findings may suggest

TABLE 2 | Effects of active psychosis and medication use on habituation and PPI percentages (median ± SEM).

	N	% Habituation				% PPI_{120ms_86dB}				% PPI_{120ms_90dB}			
	Yes/no (%)	Yes	No	*U*	*P*	Yes	No	*U*	*P*	Yes	No	*U*	*P*
Male patients (*n* = 33)													
Active psychosis[a]	5/28 (15%)	61 ± 8	57 ± 5	56.5	0.498	75 ± 32	59 ± 16	56.0	0.550	75 ± 50	79 ± 11	65.0	0.897
Medication use													
Lithium	17/16 (52%)	58 ± 5	57 ± 6	113.5	0.418	57 ± 26	64 ± 8	97.5	0.257	63 ± 21	80 ± 7	111.0	0.533
Sodium valproate	6/27(18%)	55 ± 81	58 ± 5	71.0	0.641	57 ± 34	59 ± 16	59.0	0.659	62 ± 55	79 ± 10	56.5	0.568
Lamotrigine	12/21 (36%)	59 ± 71	58 ± 5	124.5	0.955	68 ± 18	57 ± 20	91.5	0.341	80 ± 26	64 ± 13	94.5	0.404
Antidepressants	21/12 (64%)	58 ± 51	58 ± 5	113.5	0.640	59 ± 20	50 ± 17	104.0	0.648	82 ± 13	62 ± 25	86.0	0.241
Typical antipsychotics	3/30 (9%)	45 ± 18	59 ± 4	17.5	0.085	59 ± 14	59 ± 16	30.0	0.382	83 ± 11	75 ± 13	27.0	0.317
Atypical antipsychotics	16/17 (48%)	57 ± 6	58 ± 5	130.5	0.843	50 ± 28	64 ± 12	92.5	0.186	79 ± 17	75 ± 17	122	0.821
Anxiolytics/hypnotics	24/9 (73%)	57 ± 5	59 ± 6	92.5	0.531	56 ± 19	83 ± 21	67.0	0.126	64 ± 12	83 ± 31	84.0	0.413
Female patients (*n* = 54)													
Active psychosis[a]	8/46 (15%)	65 ± 9	75 ± 4	152.0	0.436	25 ± 39	67 ± 8	94.5	**0.029**	−19 ± 100	65 ± 10	103.0	**0.048**
Medication use													
Lithium	14/40 (26%)	67 ± 7	74 ± 4	246.5	0.508	54 ± 20	67 ± 11	216.5	0.209	31 ± 41	67 ± 21	238	0.401
Sodium valproate	15/39(28%)	44 ± 8	76 ± 4	187.0	**0.042**	67 ± 19	67 ± 11	267.5	0.628	44 ± 23	63 ± 24	249	0.395
Lamotrigine	6/48(11%)	67 ± 9	74 ± 4	131.0	0.720	50 ± 14	67 ± 11	100.0	0.225	−39 ± 82	62 ± 18	89.0	0.130
Antidepressants	19/35 (35%)	70 ± 7	73 ± 4	307.5	0.651	75 ± 13	57 ± 13	253.0	0.149	66 ± 14	46 ± 28	282.5	0.365
Typical antipsychotics	7/47 (13%)	70 ± 5	73 ± 4	154.0	0.787	50 ± 14	67 ± 11	120.5	0.256	0 ± 69	67 ± 19	77.5	**0.025**
Atypical antipsychotics	16/38 (30%)	61 ± 7	77 ± 4	190.5	**0.031**	71 ± 18	61 ± 11	263.5	0.442	60 ± 22	56 ± 25	288	0.755
Anxiolytics/hypnotics	30/24 (56%)	67 ± 5	78 ± 4	256.5	0.072	67 ± 12	63 ± 15	355.0	0.930	54 ± 22	56 ± 32	352.0	0.889

[a]*Active psychosis was defined as currently having either delusion of guilt, hypochondrias, or paranoia.*

Group difference was examined with the Mann–Whitney U test.

Statistical significance was set at a two-tailed p < 0.05. p-Value was not corrected. Bold figures represent significant p value.

PPI_{120ms_86dB}, prepulse inhibition (PPI) at a prepuse 120 ms; 86 dB; PPI_{120ms_90dB}, PPI at a prepuse 120 ms, 90 dB.

TABLE 3 | Spearman's correlation of clinical variables with habituation and PPI percentages.

	Habituation		PPI_{120ms_86dB}		PPI_{120ms_90dB}	
	ρ	*p*-Value	ρ	*p*-Value	ρ	*p*-Value
Male patients (*n* = 33)						
Age	0.008	0.967	0.180	0.323	0.168	0.359
Education	0.052	0.774	−0.010	0.959	−0.026	0.889
Premorbid intelligence quotient (IQ) (*n* = 29)	0.325	0.085	−0.325	0.091	−0.256	0.189
Age of onset	−0.089	0.623	0.168	0.359	0.196	0.282
Duration of illness	0.247	0.166	−0.219	0.228	−0.208	0.253
Number of hospitalization	0.002	0.990	0.176	0.335	0.291	0.106
Lithium (if any, *n* = 17)	−0.080	0.761	−0.195	0.452	0.304	0.235
Sodium valproate (if any, *n* = 6)	0.759	0.080	−0.671	0.215	−0.447	0.450
Lamotrigine (if any, *n* = 12)	−0.066	0.840	0.594	0.054	0.813	**0.002**
Antipsychotics (if any, *n* = 16)[a]	−0.056	0.836	−0.171	0.543	0.086	0.762
Typical antipsychotics (*n* = 2)	–	–	–	–	–	–
Atypical antipsychotics (*n* = 16)	−0.015	0.957	−0.257	0.354	0.007	0.980
Antidepressant (if any, *n* = 21)[b]	−0.080	0.731	−0.113	0.625	0.118	0.611
HAM-D21 total	0.077	0.668	−0.309	0.086	−0.240	0.186
YMRS total (*n* = 19)	0.145	0.554	0.267	0.284	0.336	0.172
Female patients (*n* = 54)						
Age	−0.070	0.62	−0.084	0.54	0.060	0.666
Education	−0.025	0.857	0.076	0.586	0.153	0.269
Premorid IQ (*n* = 52)	0.027	0.847	0.193	0.171	0.207	0.141
Age of onset	0.081	0.564	−0.108	0.440	0.055	0.696
Duration of illness	0.021	0.878	−0.061	0.659	−0.003	0.982
Number of hospitalization (*n* = 50)	−0.131	0.365	0.113	0.435	0.117	0.419
Lithium (if any, *n* = 14)	**−0.570**	**0.033**	**0.691**	**0.006**	0.465	0.094
Sodium valproate (if any, *n* = 15)	0.070	0.805	0.101	0.720	0.136	0.629
Lamotrigine (if any, *n* = 6)	0.304	0.558	−0.257	0.623	−0.101	0.848
Antipsychotics (if any, *n* = 21)[a]	−0.118	0.611	−0.028	0.904	0.061	0.794
Typical antipsychotics (*n* = 6)	0.257	0.623	0.600	0.208	0.371	0.468
Atypical antipsychotics (*n* = 18)	−0.220	0.380	−0.185	0.463	−0.100	0.694
Antidepressant (if any, *n* = 19)[b]	−0.193	0.427	0.309	0.199	0.202	0.407
HAM-D21 total	−0.017	0.906	−0.143	0.303	−0.253	0.065
YMRS total (*n* = 34)	−0.044	0.806	0.010	0.957	−0.086	0.631

[a]*Chlorpromazine equivalent for those who received antipsychotic medication.*

[b]*Imipramine equivalent for those who received antidepressant medication.*

Statistical significance was set at a two-tailed $p < 0.05$. Bold figures represent statistical significance.

HAM-D21, 21-item version of the Hamilton depression rating scale; YMRS, Young Mania Rating Scale; PPI_{120ms_86dB}, prepulse inhibition (PPI) at a prepuse 120 ms, 86 dB; PPI_{120ms_90dB}, PPI at a prepuse 120 ms, 90 dB.

that lamotrigine and lithium ameliorate the PPI deficits if sufficient dosage is prescribed. Our finding is in line with the previous studies reporting that lamotrigine and lithium were superior to placebo for the prevention of mood episodes in patients with BD I (75, 76). Lithium is suggested to increase inhibitory neurotransmission based on the finding that GAVA levels were increased after chronic lithium treatment (77). Alternatively, the results may have arisen by chance. Since most of the patients were treated by combined medication, interpretation of specific effects of each drug should be made with caution. Previous literature of the comparative trials on the effects of sodium valproate, haloperidol, aripiprazole, or other antipsychotics on BD patients are still limited (78–81). Some studies reported the potential ameliorating effect of a low dose of the NMDA receptor antagonist ketamine (3, 82) and L-theanine (*N*-ethyl-L-glutamine), a component of green tea, on PPI (83, 84). These findings may support a new treatment strategy on gene expression changes in glutamatergic neurotransmission and GluR expression commonly identified among schizophrenia, BD, and MDD by GWAS, postmortem brain, and magnetic resonance spectroscopy studies (29–32).

This study includes the following limitations. First, this is a cross-sectional study. Longitudinal intra-individual studies are needed to confirm the present findings and examine whether the reduced PPI in BD patients with depression is normalized in remission. Second, our results include the effects of medication. Third, the number of patients with BD I in the present study is limited (17 depressed, 9 euthymic; 25% of total patients with BD), and therefore, we were unable to examine PPI deficits exclusively in patients with BD I. Finally, we did not collect information about the history of psychosis. Although we found no correlation of startle measurements with psychopathological severity such as the age of illness onset, duration of illness, and the number of hospitalization, we were unable to analyze the effect of psychotic episodes.

In conclusion, our findings suggest that sensorimotor gating is impaired in male BD patients with depression. However, we obtained no evidence for such abnormalities in female BD

patients except for those with current psychosis. The observed associations between medication and startle measurements warrant further investigation.

ETHICS STATEMENT

This study was performed in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the National Center of Neurology and Psychiatry, Japan. Written informed consent for participation in this study was obtained from every subject.

AUTHOR CONTRIBUTIONS

JM made statistical analysis, managed literature search, interpreted the data, and wrote the draft of the manuscript. MO and SH analyzed the EMG data. MO, SH, TT, and HH conducted clinical interviews. JM, II, and MH contributed for data collection. HK supervised the entire project and gave critical comments on the manuscript. All authors contributed substantially to this work and had approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at https://www.frontiersin.org/articles/10.3389/fpsyt.2018.00123/full#supplementary-material.

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Relationship of Handgrip Strength and Body Mass Index With Cognitive Function in Patients With Schizophrenia

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Background: The relationship between muscle strength and cognition in schizophrenia has not been well studied. We investigated the potential relationship of handgrip strength (HGS) score and body mass index (BMI) with cognitive function in patients with schizophrenia.

Methods: Participants included 153 patients with schizophrenia (age: 36.9 ± 9.4 years; 82 males) and 328 healthy controls (age: 36.4 ± 10.7 years; 150 males), matched for age, sex, and ethnicity (Japanese). HGS was measured using a digital handgrip dynamometer. Cognitive function was evaluated using the Brief Assessment of Cognition in Schizophrenia (BACS) test. A two-way multivariate analysis of covariance was used to compare HGS scores between the patient and control groups. Multiple regression analyses of BACS scores were performed in the patient and control groups using HGS and BMI scores as independent variables.

Results: In the intergroup comparison, significantly lower HGS scores were observed in patients with schizophrenia than in healthy controls ($p < 0.05$, corrected). In the patient group, there was a significantly positive correlation between HGS scores and BACS composite score (male, $p = 0.0014$; female, $p = 0.0051$). However, BMI scores were significantly negatively correlated with the BACS composite score (male, $p = 0.0022$; female, $p = 0.018$). Furthermore, the ratio of HGS/BMI was significantly positively correlated with the BACS composite score in the patient group ($p = 0.00000018$).

Conclusions: Cognitive function in patients with schizophrenia is correlated positively with HGS and negatively with BMI. HGS/BMI may thus be a good index for cognitive performance in schizophrenia.

Keywords: body mass index, cognitive function, handgrip strength, schizophrenia, physical activity

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Abbreviations: ANCOVA, analysis of covariance; BACS, Brief Assessment of Cognition in Schizophrenia; BMI, body mass index; CPeq, chlorpromazine-equivalent; HGS, handgrip strength; MANCOVA, multivariate analysis of covariance; M.I.N.I., mini-international neuropsychiatric interview.

INTRODUCTION

Handgrip strength (HGS) is a concise measure used to evaluate muscle strength, and reference values have been published for healthy adults by age and sex [1, 2]. Lower HGS has been associated with sedentary lifestyle [3]. HGS is related to physical and cognitive abilities, particularly in elderly people. This relationship has been demonstrated in systematic reviews reporting that lower HGS is associated with increased risk of cognitive decline in elderly populations [4–7].

Patients with schizophrenia exhibit broad cognitive deficits in the early stages of the illness [8, 9], and physical exercise has been suggested to improve the deficits [10–13]. Light physical activity was positively correlated with cognitive performance [14], while moderate-to-vigorous physical activity was associated with greater cognitive disorganization symptoms in patients with schizophrenia [15]. Although studies regarding HGS remain scarce, lower HGS scores and exacerbated cognitive symptoms were observed in physically inactive patients with schizophrenia [16].

Body mass index (BMI) is a popular index for nutritional status [17] which has been negatively associated with moderate-to-vigorous physical activity [18]. Therefore, BMI may be associated with HGS, which is possibly attributed to physical activity levels. It has been documented that weight gain in schizophrenia can be facilitated by psychotropic medications and unhealthy lifestyle habits [19]. In line with these findings, patients with schizophrenia exhibited more sedentary behavior, which was associated with increased BMI and cognitive symptom scores [20]. In contrast, participation in sports has been demonstrated to reduce BMI and ameliorate psychiatric symptoms in patients with schizophrenia [21].

Obesity (the state of abnormally increased BMI score, BMI $\geq$ 27.5 kg/m^2) has been reported to be associated with cognitive impairments in schizophrenia [22]. The MATRICS Consensus Cognitive Battery scores were correlated positively with aerobic fitness (an index of physical ability indicated by VO_2max) and negatively with increased BMI scores in patients with schizophrenia [23]. Moreover, BMI scores correlated with Eurofit test battery scores, which are assessments of health-related fitness, but not with the HGS subtest score, in patients with schizophrenia or schizoaffective disorder [24]. In addition, [16] reported no correlation between HGS score and cognitive symptoms in a non-elderly sample of patients with schizophrenia (n = 80) and healthy adult controls (n = 40).

Based on the reported associations between physical and cognitive abilities, it is of particular interest to examine the possible relationship between HGS and cognitive performance in patients with schizophrenia. We aimed to assess this relationship by using the Brief Assessment of Cognition in Schizophrenia (BACS) in a relatively large sample of patients with schizophrenia and healthy controls. It was hypothesized that there would be a positive correlation between HGS score and cognitive function.

MATERIALS AND METHODS

Participants

Participants comprised 153 patients with schizophrenia (mean $\pm$ standard deviation age: 36.9 $\pm$ 9.4 years, 82 males) and 328 healthy controls (36.4 $\pm$ 10.7 years, 150 males), matched for age, sex, and ethnicity (Japanese). To exclude the possible effect of aging, only those who were <60 years old were registered. All the participants were self-reported right-handers, and were enrolled through recruitment forms at the National Center of Neurology and Psychiatry, advertisements in free magazines, and our website announcement. The participants were screened for axis I psychiatric disorders by trained psychiatrists using the Japanese version of the Mini-International Neuropsychiatric Interview (M.I.N.I.) [25, 26]. The diagnosis was made in accordance with the Diagnostic and Statistical Manual of Mental Disorders-4th edition criteria [27] based on the information from M.I.N.I. and medical records, if available. All healthy controls were confirmed to have no axis I psychiatric disorders and to have never received psychiatric services. Patients and controls with a medical history of neurological diseases, severe head injury, substance abuse, or mental retardation were excluded. All participants signed consent forms after the study explanation. The study protocol was approved by the ethics committee at the National Center of Neurology and Psychiatry, and applied according to the Declaration of Helsinki [28].

Clinical and Psychological Assessments

HGS was measured using a digital handgrip dynamometer (T.K.K.5401; Takei Co., Tokyo, Japan). Right (dominant) and left (non-dominant) HGSs were calculated for each participant by taking the mean of two records conducted for each hand. The average HGS was then calculated for each participant by taking the mean of the dominant and non-dominant HGSs. The severity of symptoms in the patients was evaluated by trained psychiatrists using the Japanese adaptation of the Positive and Negative Syndrome Scale [29, 30]. Cognitive functions were evaluated by trained psychologists using the Japanese version of the BACS [31, 32]. The BACS composite score was the mean z score calculated from each BACS score, based on the mean and standard deviation of the healthy controls. Daily doses of antipsychotics were converted to chlorpromazine-equivalent (CPeq) doses according to published guidelines [33].

Statistical Analyses

Continuous and categorical variables were compared between the patient and control groups using Welch's t- and chi-square tests, respectively. Correlations for continuous and categorical variables were calculated using Pearson's and Spearman's correlation coefficients, respectively. BACS scores were compared using a one-way (diagnostic) multivariate analysis of covariance (MANCOVA), controlling for age, sex, and BMI. HGS scores were compared using a two-way (diagnosis x sex) MANCOVA, controlling for age and BMI. Comparisons of average HGS among BMI-based classification groups (underweight: BMI < 18.5, normal: 18.5 $\leq$ BMI < 25, overweight: 25 $\leq$ BMI < 30, obese: BMI $\geq$ 30) [34] were conducted using analysis of

covariance (ANCOVA), controlling for age and sex. CPeq and any psychotropic medication use were accounted for in the patient group. Multiple regression analyses were performed using the BACS scores as dependent variables and applying independent variables by the forced-entry method. Bonferroni corrections for multiple testing were performed for all the group comparisons, correlations, and multiple regression analyses. For instance, as correlations and multiple regression analyses were repeated with regard to all seven BACS scores, the statistical significance level was set to $p < 0.05/7$. Effect sizes were calculated by Cohen's d for the *t*-test, ϕ for the chi-square test, η^2 for the ANCOVA and MANCOVA, and adjusted R^2 for the multiple regression analysis. Statistical analyses were conducted using the Statistical Package for the Social Sciences version 24.0 (SPSS Japan, Tokyo, Japan). All statistical tests were two-tailed, and a *p*-value of <0.05 was deemed significant.

RESULTS

Analyses of Clinical Variables

Demographic and clinical characteristics of the participants are depicted in **Table 1**. Mean BMI was significantly higher in patients with schizophrenia than in healthy controls after correction for multiple testing. With regard to BMI-based classification, the proportion of normal participants was significantly lower (odds ratio = 0.45, 95% confidence interval: 0.30–0.68), while that of obese participants was significantly higher in the patient group than in the control group (odds ratio = 4.52, 95% confidence interval: 2.00–10.40; corrected). A MANCOVA analysis revealed that all of the BACS scores were significantly lower in the patient group than in the control group (corrected).

Analyses of HGS Scores

HGS scores of the participants are depicted in **Table 2**. A two-way MANCOVA revealed that all HGS scores were significantly lower in the patient group than in the control group, and were significantly higher in males than in females (corrected). The average HGS (i.e., the average of left and right HGS scores) was used as "the HGS score" in the following analyses. Correlations between HGS score and clinical variables are demonstrated in Table S1. Of note, BMI was significantly positively correlated with HGS score in both groups (patient: $r = 0.27$, $p = 8.0.E-04$; control: $r = 0.40$, $p = 3.4.E-14$). Comparisons of HGS scores by BMI-based classification are displayed in Figure S1.

Correlation of HGS and BMI Scores With Cognitive Function

Multiple regression analysis for each sex involving BACS scores and forced-entry variables are documented in **Table 3**. BACS scores were used as dependent variables, while HGS scores, age, BMI, education (years), CPeq (for patients), and any psychotropic medication use (for patients) were used as independent variables. Attention ($\beta = 0.47$, $p = 4.0.E-05$) and composite ($\beta = 0.36$, $p = 1.4.E-03$) scores were significantly positively correlated with HGS scores in male patients (corrected). Motor speed ($\beta = 0.34$, $p = 1.5.E-03$), attention ($\beta = 0.36$, $p = 1.4.E-03$), and composite ($\beta = 0.30$, $p = 5.1.E-03$) scores were significantly positively correlated with HGS scores in female patients (corrected). Motor speed ($\beta = -0.40$, $p = 1.3.E-03$) and composite ($\beta = -0.36$, $p = 2.2.E-03$) scores were significantly negatively correlated with BMI in male patients (corrected). Working memory was significantly negatively correlated with BMI in female patients ($\beta = -0.34$, $p = 6.9.E-03$, corrected). No significant correlations were observed between the HGS and BACS scores in male or female controls. However, working memory ($\beta = -0.21$, $p = 5.8.E-03$) and composite ($\beta = -0.22$, $p = 2.8.E-03$) scores were significantly negatively correlated with BMI in female controls (corrected).

Based on these results, further multiple regression analysis was conducted using a newly-defined index, namely the ratio of HGS to BMI (**Table 4**). BACS scores were used as dependent variables, while HGS/BMI, age, sex, education (years), CPeq (for patients), and any psychotropic medication use (for patients), were used as independent variables. In this case, working memory ($\beta = 0.35$, $p = 9.7.E-04$), motor speed ($\beta = 0.47$, $p = 1.2.E-05$), verbal fluency ($\beta = 0.40$, $p = 2.3.E-04$), attention ($\beta = 0.56$, $p = 2.9.E-08$), and composite ($\beta = 0.51$, $p = 1.8.E-07$) scores were significantly positively correlated with HGS/BMI in the patient group (corrected). Composite score was significantly positively correlated with HGS/BMI in the control group ($\beta = 0.20$, $p = 2.6.E-03$, corrected).

Correlation Between Cognitive Function and Clinical Variables

Correlations between the BACS scores and clinical variables are documented in Table S2. In bivariate correlation analyses, attention ($r = 0.23$, $p = 3.5.E-03$) and composite ($r = 0.25$, $p = 2.3.E-03$) scores were significantly positively correlated with HGS score in the patient group (corrected). Verbal memory ($r = -0.26$, $p = 1.5.E-03$), working memory ($r = -0.30$, $p = 2.2.E-04$), motor speed ($r = -0.28$, $p = 6.1.E-04$), verbal fluency ($r = -0.26$, $p = 1.1.E-03$), attention ($r = -0.27$, $p = 7.8.E-04$), and composite ($r = -0.33$, $p = 4.4.E-05$) scores were significantly negatively correlated with BMI in the patient group (corrected). Notably, all of the BACS scores were significantly positively correlated with HGS/BMI in the patient group (**Figure 1**, corrected). In the control group, BACS scores were not significantly correlated with HGS score. However; verbal memory ($r = -0.24$, $p = 7.9.E-06$), working memory ($r = -0.21$, $p = 1.6.E-04$), attention ($r = -0.27$, $p = 5.5.E-07$), and composite ($r = -0.28$, $p = 4.3.E-07$) scores were significantly negatively correlated with BMI in the control group (corrected). By contrast, only working memory score showed a significantly positive correlation with HGS/BMI in the control group (**Figure 2**, corrected).

DISCUSSION

The present study examined the association of HGS and BMI with cognitive function. HGS scores were significantly reduced in patients with schizophrenia compared to healthy controls. The HGS and BMI scores and the HGS/BMI were significantly associated with cognitive impairments in

TABLE 1 | Demographic and clinical characteristics of the participants.

	Patients with schizophrenia ($n = 153$)		Healthy controls ($n = 328$)		
	Mean ± Standard deviation	**Range**	**Mean ± Standard deviation**	**Range**	**Statistical comparison**
Age (years)	36.9 ± 9.4	18-58	36.4 ± 10.7	18–59	$t_{(334.7)} = -0.49$, $p = 0.63$, Cohen's d = 0.05
Sex, male (%)	82 (53.6)		150 (45.7)		$\chi^2_{(1)} = 2.58$, $p = 0.11$, $\phi = -0.07$
Education (years)	14.0 ± 2.4	9–22	15.1 ± 2.1	9–22	$t_{(267.1)} = 5.02$, $\mathbf{p = 9.4.E-07}$, Cohen's d =0.51
Body mass idex (kg/m^2)	24.3 ± 5.1	14.3–45.2	22.1 ± 3.4	15.8–34.3	$t_{(209.5)} = -4.68$, $\mathbf{p = 5.0.E-06}$, Cohen's d = 0.54
Underweight	15 (9.8)		26 (7.9)		$\chi^2_{(1)} = 0.55$, $p = 0.46$, $\phi = 0.03$
Normal	85 (55.5)		43 (74.1)		$\chi^2_{(1)} = 15.05$, $\mathbf{p = 1.0.E-04}$, $\phi = -0.18$ OR = 0.45, 95%CI:0.30-0.68
Overweight	32 (20.9)		47 (14.3)		$\chi^2_{(1)} = 3.62$, $p = 0.057$, $\phi = 0.09$
Obese	17 (11.1)		9 (2.7)		$\chi^2_{(1)} = 14.71$, $\mathbf{p = 1.3.E-04}$, $\phi = 0.18$ OR = 4.52, 95%CI:2.00-10.40
BACS					
Verbal memory	40.6 ± 12.8	10–71	51.5 ± 9.6	20–75	$F_{(1,468)} = 89.34$, $\mathbf{p = 1.6.E-19}$, $\eta^2 = 0.13$
Working memory	18.7 ± 4.5	8–28	22.1 ± 3.7	10–28	$F_{(1,468)} = 61.50$, $\mathbf{p = 3.0.E-14}$, $\eta^2 = 0.10$
Motor speed	70.7 ± 16.4	22–100	83.4 ± 12.1	40–100	$F_{(1,468)} = 70.17$, $\mathbf{p = 6.4.E-16}$, $\eta^2 = 0.12$
Verbal fluency	43.5 ± 12.3	14–76	51.8 ± 10.3	26–87	$F_{(1,468)} = 41.10$, $\mathbf{p = 3.5.E-10}$, $\eta^2 = 0.08$
Attention	54.4 ± 13.3	19–86	72.1 ± 12.9	37–100	$F_{(1,468)} = 174.18$, $\mathbf{p = 4.9.E-34}$, $\eta^2 = 0.22$
Executive function	16.7 ± 3.4	4–22	18.3 ± 2.6	3–22	$F_{(1,468)} = 26.64$, $\mathbf{p = 3.6.E-07}$, $\eta^2 = 0.05$
Composite	−1.00 ± 0.9	−3.89–1.01	0.00 ± 0.6	−1.94–1.50	$F_{(1,468)} = 168.50$, $\mathbf{p = 4.0.E-33}$, $\eta^2 = 0.22$
Age of onset (years)	23.1 ± 7.2	5–54			
Duration of illness (years)	13.7 ± 8.9	1–38			
CPeq (mg/day)					
Typical antipsychotics	95.8 ± 220.7	0–1362.5			
Atypical antipsychotics	349.3 ± 375.7	0–1860			
Total antipsychotics	445.2 ± 410.3	0–1960			
Antiparkinson medication use (%)	57 (37.3)				
Minor tranquilizer use (%)	89 (58.2)				
Any psychotropic medication use (%)	131 (85.6)				
PANSS					
Positive	13.6 ± 5.0	7–32			
Negative	15.8 ± 6.1	7–33			
General psychopathology	29.9 ± 8.3	16–53			

BACS, Brief Assessment of Cognition in Schizophrenia; CI, confidence interval; CPeq, chlorpromazine-equivalent dose; OR, odds ratio; PANSS, Positive and Negative Syndrome Scale. Significant p-values ($p < 0.016$ for the t-test, $p < 0.01$ for the chi-square test, and $p < 0.007$ for the multivariate analysis of covariance, corrected for multiple testing) are shown in bold exponents. There were 4 and 3 missing values of BMI scores in the patients and controls, respectively.

the patient group. However, the HGS/BMI was significantly associated with only the BACS composite score in the control group. Our findings suggest that HGS and BMI have positive and negative relationships, respectively, with cognitive function in both male and female patients with schizophrenia.

We found that patients with schizophrenia obtained lower HGS scores than in healthy controls, irrespective of sex or BMI. The HGS scores exhibited a positive correlation with the BACS motor speed, attention, and composite scores in the patient group. A previous study reported no correlation between HGS and cognitive scores measured by the psychosis evaluation tool for common use by caregivers [16]. In contrast, the current study demonstrates for the first time several correlations between HGS and cognitive measures using a comprehensive cognitive battery. Our results suggest a positive relationship between HGS and cognitive function in patients with schizophrenia under the age of 60 years. As reported with regard to elderly cognitive decline [4–7], HGS may be used as an additional index to reflect cognitive deficits in schizophrenia, particularly deficits of motor speed and

TABLE 2 | Handgrip strength scores of the participants.

	Male				Female				
	Patient (n = 82)		Control (n = 150)		Patient (n = 71)		Control (n = 178)		Statistical comparison
	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD	Range	For diagnosis
Average hangrip strength (kg)	35.9 ± 7.4	16.4–52.0	38.0 ± 6.1	22.6–52.2	22.8 ± 4.7	9.5–41.9	24.9 ± 4.3	13.8–39.2	$F_{(1,468)} = 27.0$, $\mathbf{p = 3.0E\text{-}07}$, $\eta^2 = 0.023$
Right handgrip strength (kg)	37.0 ± 7.6	18.1–55.2	38.9 ± 6.4	24.7–55.0	23.2 ± 5.4	8.0–45.3	25.7 ± 4.6	10.9–41.7	$F_{(1,468)} = 24.2$, $\mathbf{p = 1.7E\text{-}06}$, $\eta^2 = 0.022$
Left handgrip strength (kg)	34.8 ± 7.7	13.0–48.8	37.1 ± 6.3	20.5–51.8	22.3 ± 4.4	10.9–38.6	24.2 ± 4.4	12.5–36.8	$F_{(1,468)} = 25.2$, $\mathbf{p = 7.2E\text{-}08}$, $\eta^2 = 0.021$

SD, standard deviation. Significant p-values ($p < 0.016$; corrected for multiple testing) are shown in bold exponents.
There was no significant interaction between diagnosis and sex ($p = 0.64$ for the average, $p = 0.35$ for the right, and $p = 0.96$ for the left handgrip strength scores, respectively).

attention. These deficits may be influenced by physical activity levels [14, 15].

BMI was negatively correlated with the BACS working memory, motor speed, and composite scores in the patient group. These correlations agree with prior findings [22, 23], and with our recent study reporting that obesity is associated with poorer cognitive function in patients with major depressive disorder [35]. Increased BMI in schizophrenia may be associated with lower physical activity levels [20, 23], although our data did not take physical activity into account. In addition, we observed a positive correlation between BMI and HGS scores in both the patient and control groups. These findings are in contrast with previous findings in patients with schizophrenia or schizoaffective disorder [24]. However, similar results to ours have been obtained in healthy controls [2, 36]. In addition, our BMI-based comparisons showed that higher and lower HGS scores were observed in obese and underweight participants, respectively. Taking the relationships of both HGS and BMI scores into consideration, the optimal BMI range (i.e., normal) may be beneficial for cognitive function in schizophrenia.

The ratio of HGS/BMI is a newly-defined index based on the former regression analyses. This ratio positively correlated with the BACS working memory, motor speed, verbal fluency, attention, and composite scores in the patient group. Furthermore, in bivariate correlation analyses, the ratio positively correlated with all BACS scores in the patients. These results suggest that the HGS/BMI could be a concise and useful index to estimate the level of cognitive performance in schizophrenia. In this context, higher HGS and lower BMI scores may contribute to the promotion of schizophrenic cognitive function. With regard to treatment, interventions for HGS and BMI using physical exercise have the potential to ameliorate cognitive dysfunctions in patients with schizophrenia. Such effects have previously been reported in cases of dementia [37, 38] and schizophrenia [39–42]. Considering the positive correlation between HGS and BMI scores, it is highly plausible that the balance of high HGS and low BMI scores, namely a higher HGS relative to BMI may be preferable for cognitive performance in schizophrenia.

Multiple regression analyses revealed that there were no effects of HGS on cognitive function, while the HGS/BMI was positively correlated with only the composite score in healthy controls. Notably, the HGS/BMI was positively associated with cognitive function in healthy controls, although the associations appeared to be weaker compared to patients with schizophrenia. Ceiling effects may contribute to the weaker association, as HGS and BACS scores were higher and BMI scores were lower in controls compared to patients. Moreover, specialized interactions between physical ability and cognitive function may be present in patients with schizophrenia, as suggested by previous studies [10–13]. Lifestyle factors observed in patients with schizophrenia [19], such as lower physical activity levels and higher BMI, may have influenced the difference between the patients and controls. Indeed, patients with schizophrenia were reported to be physically inactive compared to healthy controls [16], although data related to physical activity were not included in the present study.

This study had several limitations. First, the majority of the patients (85.7%) had taken psychotropic medications. These effects were accounted for by the ANCOVA and multiple regression analyses. Second, we conducted corrections for multiple testing using the Bonferroni method which may have resulted in type II errors due to the conservative nature of the analysis. Lastly, the cross-sectional approach of the current study cannot draw any conclusions concerning causal relationships. Given the correlational nature of the analysis, we cannot clarify whether cognitive dysfunction is the cause or result of low HGS in schizophrenia. It is possible that physical disabilities and cognitive deficits have individual and negative impacts on daily functioning in schizophrenia. This theory is supported by the therapeutic effects of aerobic exercise on brain structure and function via neuroplastic changes in patients with schizophrenia [43–46].

In conclusion, patients with schizophrenia showed lower HGS scores compared to healthy controls. In the patient group, HGS and BMI scores correlated positively and negatively with cognitive functions, respectively. Furthermore, the ratio of HGS/BMI positively correlated with the majority of the cognitive functions examined in the patient group. HGS/BMI may thus be a good index for cognitive performance in schizophrenia. These results suggest that a close relationship exists between physical status (muscle strength and BMI) and cognitive function in patients with schizophrenia.

TABLE 3 | Multiple regression analysis for each sex involving Brief Assessment of Cognition in Schizophrenia (BACS) scores and forced-entry variables.

	Verbal memory		Working memory		Motor speed		Verbal fluency		Attention		Executive function		Composite	
	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*
<Male patients>	$R^2 = 0.09$		$R^2 = 0.08$		$R^2 = 0.16$		$R^2 = 0.18$		$R^2 = 0.29$		$R^2 = 0.003$		$R^2 = 0.27$	
Handgrip strength (kg)	0.15	0.21	0.16	0.19	0.29	0.01	0.23	0.05	0.47	**4.0E-05**	0.10	0.44	0.36	**1.4E-03**
Age (years)	−0.13	0.29	−0.10	0.41	0.10	0.41	0.11	0.35	−0.14	0.21	0.08	0.51	−0.02	0.86
Education (years)	0.15	0.22	0.15	0.23	−0.04	0.72	−0.05	0.68	0.08	0.48	0.02	0.87	0.08	0.47
Body mass idex (kg/m^2)	−0.22	0.09	−0.23	0.07	−0.40	**1.3.E-03**	−0.29	0.02	−0.26	0.02	−0.11	0.39	−0.36	**2.2E-03**
CPeq total antipsychotics (mg/day)	−0.11	0.36	−0.05	0.67	−0.19	0.12	0.01	0.91	−0.07	0.50	0.10	0.42	−0.07	0.50
Any psychotropic medication use (%)	−0.09	0.48	−0.11	0.40	0.09	0.47	−0.34	**5.9.E-03**	−0.14	0.20	−0.26	0.05	−0.21	0.06
<Female patients>	$R^2 = 0.25$		$R^2 = 0.22$		$R^2 = 0.35$		$R^2 = 0.13$		$R^2 = 0.30$		$R^2 = 0.16$		$R^2 = 0.37$	
Handgrip strength (kg)	0.16	0.16	0.10	0.36	0.34	**1.5E-03**	0.25	0.04	0.36	**1.4E-03**	0.16	0.18	0.30	**5.1.E-03**
Age (years)	−0.35	**2.5.E-03**	−0.19	0.10	0.05	0.61	−0.06	0.60	−0.14	0.19	−0.19	0.11	−0.20	0.05
Education (years)	0.26	0.03	0.17	0.16	0.21	0.05	0.25	0.04	0.14	0.21	0.00	0.98	0.22	0.04
Body mass idex (kg/m^2)	−0.16	0.17	−0.34	**6.9.E-03**	−0.15	0.18	−0.25	0.05	−0.29	0.01	−0.05	0.69	−0.26	0.02
CPeq total antipsychotics (mg/day)	−0.09	0.45	−0.17	0.18	−0.17	0.14	0.02	0.89	−0.22	0.07	−0.37	**6.9.E-03**	−0.23	0.05
Any psychotropic medication use (%)	−0.11	0.38	−0.05	0.73	−0.32	0.01	−0.06	0.68	−0.06	0.65	−0.03	0.82	−0.14	0.25
<Male controls>	$R^2 = 0.24$		$R^2 = 0.24$		$R^2 = 0.13$		$R^2 = 0.08$		$R^2 = 0.32$		$R^2 = 0.04$		$R^2 = 0.28$	
Handgrip strength (kg)	0.01	0.89	0.01	0.89	0.03	0.70	−0.01	0.89	−0.01	0.93	0.12	0.14	0.04	0.63
Age (years)	−0.46	**3.9.E-08**	−0.46	**3.9.E-08**	−0.23	0.01	−0.06	0.48	−0.49	**1.0.E-09**	−0.16	0.08	−0.36	**6.4.E-06**
Education (years)	−0.11	0.16	0.03	0.72	0.19	0.01	0.24	**3.5.E-03**	0.16	0.02	0.13	0.11	0.27	**2.9E-04**
Body mass idex (kg/m^2)	0.03	0.72	−0.11	0.16	−0.16	0.07	−0.08	0.37	−0.09	0.23	−0.03	0.71	−0.15	0.06
<Female controls>	$R^2 = 0.10$		$R^2 = 0.08$		$R^2 = 0.00$		$R^2 = 0.08$		$R^2 = 0.17$		$R^2 = 0.05$		$R^2 = 0.19$	
Handgrip strength (kg)	0.04	0.60	0.04	0.58	0.07	0.39	0.14	0.06	0.15	0.04	0.06	0.46	0.14	0.06
Age (years)	−0.23	**4.8.E-03**	−0.10	0.23	0.00	0.97	0.10	0.25	−0.20	0.01	−0.02	0.77	−0.12	0.11
Education (years)	0.17	0.04	0.14	0.08	0.01	0.88	0.27	**9.3.E-04**	0.24	**2.2.E-03**	0.23	**5.4.E-03**	0.29	**1.5E-04**
Body mass idex (kg/m^2)	−0.06	0.44	−0.21	**5.8.E-03**	−0.15	0.06	−0.12	0.11	−0.17	0.02	−0.07	0.38	−0.22	**2.8.E-03**

CPeq, chlorpromazine-equivalent dose. Significant p-values ($p < 0.0071$; corrected for multiple testing) are shown in bold exponents.

TABLE 4 | Multiple regression analysis between Brief Assessment of Cognition in Schizophrenia (BACS) scores and handgrip strength/body mass index.

	Verbal memory		Working memory		Motor speed		Verbal fluency		Attention		Executive function		Composite	
	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*
<Patients with schizophrenia>	$R^2 = 0.19$		$R^2 = 0.19$		$R^2 = 0.23$		$R^2 = 0.15$		$R^2 = 0.32$		$R^2 = 0.09$		$R^2 = 0.35$	
Handgrip strength/body mass index (m^2)	0.26	0.01	0.35	**9.7.E-04**	0.47	**1.2E-05**	0.40	**2.3.E-04**	0.56	**2.9E-08**	0.15	0.17	0.51	**1.8E-07**
Age (years)	−0.26	**1.7.E-03**	−0.14	0.08	0.06	0.47	0.01	0.91	−0.14	0.06	−0.07	0.39	−0.13	0.08
Sex	0.19	0.07	0.06	0.53	0.38	**2.0.E-04**	0.21	0.05	0.37	**9.4E-05**	−0.11	0.29	0.26	**4.6.E-03**
Education (years)	0.22	0.01	0.17	0.04	0.07	0.36	0.10	0.21	0.12	0.12	0.04	0.65	0.17	0.02
CPeq total antipsychotics (mg/day)	−0.10	0.24	−0.08	0.33	−0.17	0.04	0.01	0.91	−0.13	0.10	−0.10	0.27	−0.13	0.09
Any psychotropic medication use (%)	−0.10	0.25	−0.10	0.25	−0.09	0.30	−0.18	0.04	−0.07	0.37	−0.15	0.10	−0.16	0.04
<Healthy controls>	$R^2 = 0.19$		$R^2 = 0.09$		$R^2 = 0.02$		$R^2 = 0.08$		$R^2 = 0.25$		$R^2 = 0.06$		$R^2 = 0.22$	
Handgrip strength / body mass index (m^2)	0.10	0.15	0.14	0.04	0.10	0.19	0.13	0.08	0.17	0.01	0.12	0.10	0.20	**2.6.E-03**
Age (years)	−0.37	**5.7.E-12**	−0.20	**3.7.E-04**	0.00	0.98	0.00	0.93	−0.37	**9.9.E-13**	−0.09	0.12	−0.28	**1.3.E-07**
Sex	0.25	**2.3.E-04**	0.07	0.35	0.10	0.19	0.24	**1.1.E-03**	0.27	**4.5.E-05**	0.02	0.78	0.25	**1.7.E-04**
Education (years)	0.08	0.12	0.16	**4.8.E-03**	0.15	0.01	0.25	**1.2.E-05**	0.18	**3.1.E-04**	0.18	**1.6.E-03**	0.27	**3.7.E-07**

CPeq, chlorpromazine-equivalent dose. Significant p-values ($p < 0.0071$; corrected for multiple testing) are shown in bold exponents. Sex was coded as male: 1 and female: 2.

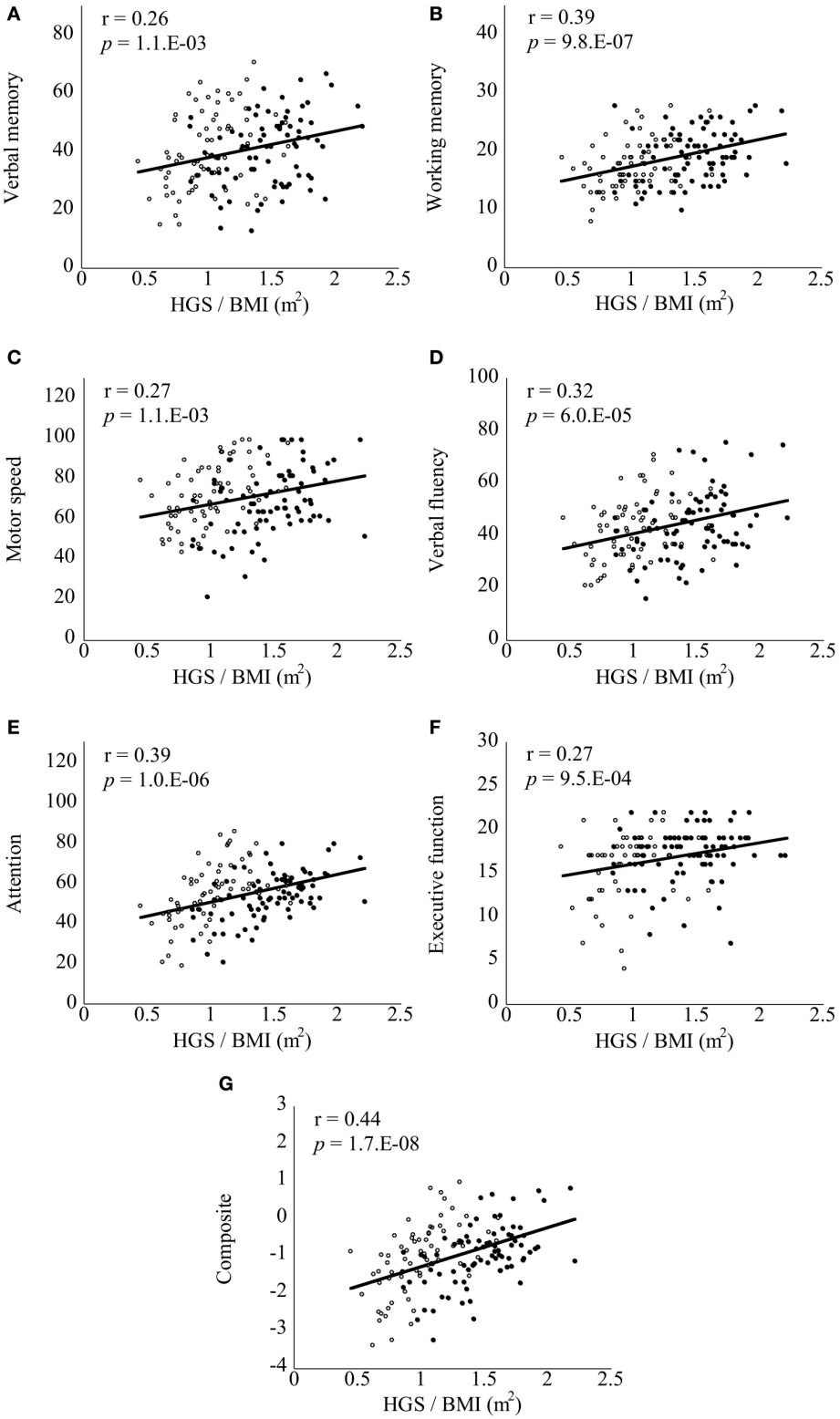

FIGURE 1 | Scatter plots of correlations between handgrip strength (HGS)/body mass index (BMI) and Brief Assessment of Cognition in Schizophrenia (BACS) scores in patients with schizophrenia. HGS/BMI positively correlated with all of the BACS scores **(A–G)** in the patients with schizophrenia (all $p < 0.0071$, corrected for multiple testing). Black and white circles indicate male and female patients, respectively. Significant *p*-values are shown in exponents. r, Pearson's correlation coefficient.

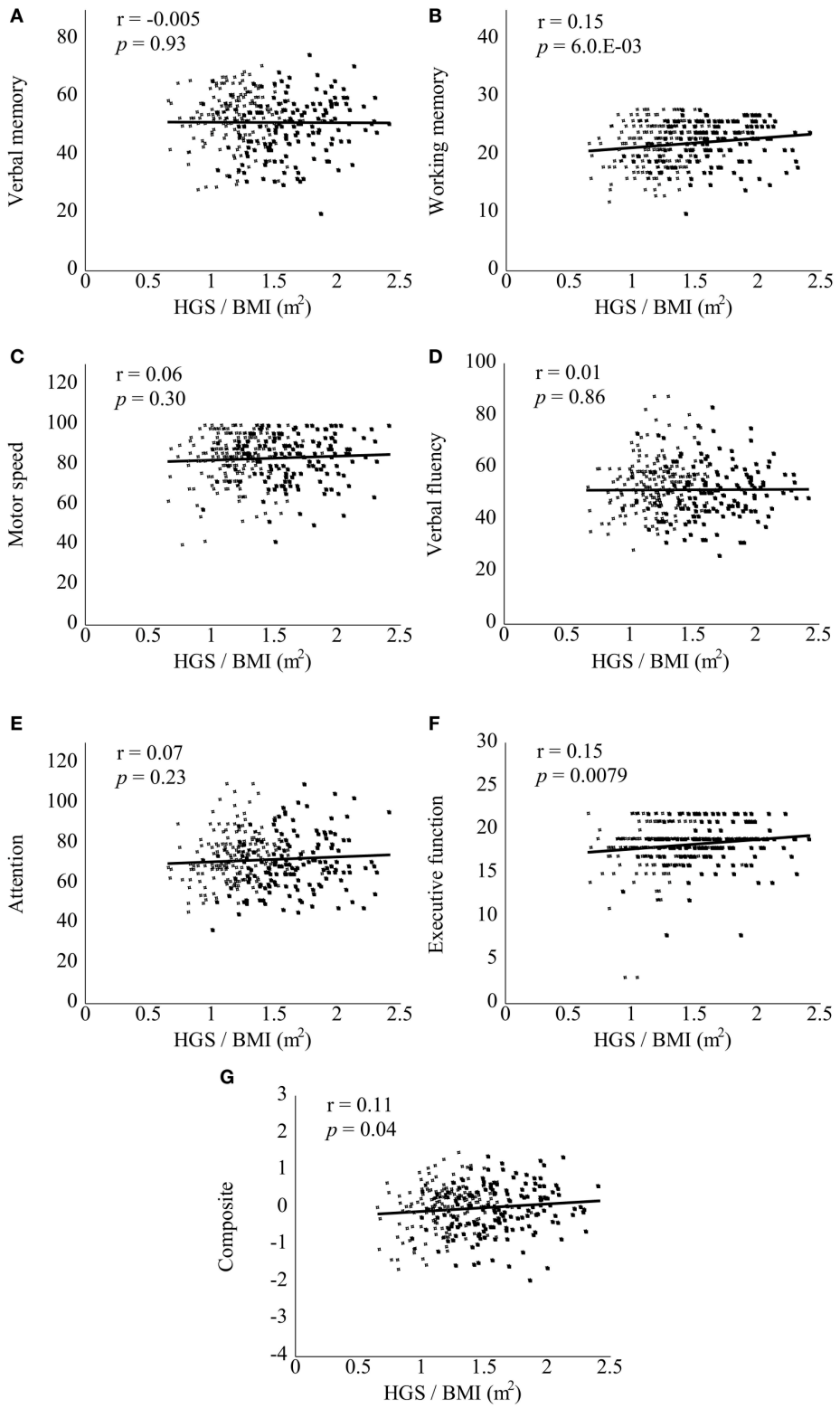

FIGURE 2 | Scatter plots of correlations between handgrip strength (HGS)/body mass index (BMI) and Brief Assessment of Cognition in Schizophrenia (BACS) scores in healthy controls. HGS/BMI positively correlated with only the BACS working memory score (**B**, not **A** or **C–G**) in the controls ($p < 0.0071$, corrected for multiple testing). Black and white squares indicate male and female controls, respectively. A significant *p*-value is shown in an exponent. r, Pearson's correlation coefficient.

AUTHORS CONTRIBUTIONS

SH designed, and HK supervised the study; JM, II, and MH assessed cognitive function by the BACS. SH, TT, MO, and KH determined psychiatric diagnoses and evaluated symptoms by the Positive and Negative Syndrome Scale; SH performed the statistical analysis and wrote the draft of the manuscript. All authors have approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2018.00156/full#supplementary-material

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REVIEW
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Early Intervention and a Direction of Novel Therapeutics for the Improvement of Functional Outcomes in Schizophrenia: A Selective Review

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Background: A recent review reported that the median proportion of patients recovering from schizophrenia was 13.5% and that this did not change over time. Various factors including the duration of untreated psychosis, cognitive impairment, negative symptoms, and morphological changes in the brain influence the functional outcome of schizophrenia. The authors herein reviewed morphological changes in the brain of schizophrenia patients, effects of early intervention, and a direction of developing novel therapeutics to achieve significant improvement of the functional outcome.

Methods: A selective review of the literature including studies from our department was performed.

Results: Longitudinal structural neuroimaging studies on schizophrenia revealed that volume reductions in the peri-Sylvian regions (e.g., superior temporal gyrus and insula), which are related to positive psychotic symptoms, progress around the onset (critical stage) of schizophrenia, but become stable in the chronic stage. On the other hand, morphological changes in the fronto-thalamic regions and lateral ventricle, which are related to negative symptoms, neurocognitive dysfunction, and the functional outcome, progress during both the critical and chronic stages. These changes in the peri-Sylvian and fronto-thalamic regions may provide a pathophysiological basis for Crow's two-syndrome classification. Accumulated evidence from early intervention trials suggests that the transition risk from an at-risk mental state (ARMS) to psychosis is approximately 30%. Differences in the cognitive performance, event-related potentials (e.g., mismatch negativity), and brain morphology have been reported between ARMS subjects who later developed psychosis and those who did not. Whether early intervention for ARMS significantly improves the long-term recovery rate of schizophrenia patients remains unknown. With respect to the development of novel therapeutics, animal models of schizophrenia based on the *N*-methyl-D-aspartate receptor hypofunction hypothesis successfully mimicked behavioral changes associated with cognitive impairments

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characteristic of the disease. Furthermore, these animal models elicited histological changes in the brain similar to those observed in schizophrenia patients, i.e., decreased numbers of parvalbumin-positive interneurons and dendritic spines of pyramidal neurons in the frontal cortex. Some antioxidant compounds were found to ameliorate these behavioral and histological abnormalities.

Conclusion: Early intervention coupled with novel therapeutics may offer a promising approach for substantial improvement of the functional outcome of schizophrenia patients.

Keywords: schizophrenia, functional outcome, early intervention, *N*-methyl-D-aspartate receptor, structural MRI

INTRODUCTION

The functional outcome of schizophrenia patients has been a major concern in psychiatry. A systematic review of 50 studies from 1921 to 2011 (1) demonstrated that the median proportion of patients recovering from schizophrenia was 13.5% and that this did not change over time despite the progress in treatment in recent decades.

Various factors have been reported to influence the course and outcome of schizophrenia patients. The predictors of the 2-year outcome in the WHO 10-country study (2) were the age, sex, marital status, mode of onset (acute or insidious), duration of untreated psychosis (DUP), premorbid psychosocial functioning, close friends, drug abuse, and sociocultural setting, i.e., a developing versus a developed country. However, most of these factors except DUP and drug abuse are beyond clinical control.

Other important factors include neurocognitive dysfunctions (3–6), negative symptoms (7, 8), and alterations in brain morphology (9–11). Although antipsychotic medications are effective for reducing positive psychotic symptoms, these symptoms including first-rank symptoms showed no significant correlation with the outcome of schizophrenia patients (2, 3). The improvements of cognitive impairment and negative symptoms are not satisfactory with the current treatment, and they may have pathophysiologies that differ from those of positive symptoms. It should be noted that there is compelling evidence that the progressive enlargement of the lateral ventricles is closely related to the outcome of schizophrenia patients (9–11). These morphological brain changes should be the target of novel therapeutics.

Duration of untreated psychosis, neurocognitive dysfunctions, negative symptoms, and brain morphology are potentially controllable by medicine. An effective method to substantially improve the functional outcome would be to develop a therapeutic strategy to control these factors. Therefore, the authors reviewed studies on morphological changes in the brain of schizophrenia patients, early intervention, and a direction of developing novel therapeutics.

METHODS

The method was a selective review of the literature including studies from the authors' department. Concerning studies on morphological brain changes associated with functional outcome in schizophrenia patients, the authors searched PubMed using the keywords: "MRI," "functional outcome," and "schizophrenia." Combination with the author's previous manual list resulted in 15 publications relevant to the present theme as shown in **Table 1**. Some of these studies were the starting point of this review. In the section of novel therapeutics, potential candidate compounds are described, capable of ameliorating the histological brain changes in schizophrenia patients.

STRUCTURAL MAGNETIC RESONANCE IMAGING STUDIES ON SCHIZOPHRENIA

Region of Interest Method

Structural magnetic resonance imaging (sMRI) studies using the region of interest method have demonstrated significant volume reductions in schizophrenia patients mainly in three brain regions: the medial temporal lobe structures (hippocampus and amygdala), peri-Sylvian regions (superior temporal gyrus and insula), and prefrontal areas including fronto-thalamic connections, compared with healthy control subjects. We noted the difference in brain morphology between patients with schizophrenia and subjects with schizotypal (personality) disorder or first-degree relatives of the patients to differentiate the disease process from risk- or vulnerability-associated changes.

Among the three regions, volume reductions in the medial temporal lobe structures have been confirmed in schizophrenia patients (24). However, these changes may represent a risk of or vulnerability to the disease, as pointed out by Seidman et al. (25), since these changes were also seen to the same extent in schizotypal (personality) disorder and first-degree relatives of patients with schizophrenia (25–27). A meta-analysis of longitudinal sMRI studies on schizophrenia (28) showed no evidence to suggest progressive medial temporal lobe involvement.

Volume reductions in the superior temporal gyrus were seen in both schizophrenia and schizotypal disorder patients (29, 30). However, the changes in schizophrenia patients were more widespread than in schizotypal disorder patients: the changes extended to Heshcl's gyrus and the planum polare in schizophrenia, but not in schizotypal disorder (30). In longitudinal studies, progressive decreases in the gray matter volume in the left superior temporal gyrus were noted in first-episode schizophrenia patients (31, 32). During the chronic stage, however, no significant progressive changes of the superior temporal gyrus were seen in schizophrenia patients using the region of interest method (33, 34).

TABLE 1 | Morphological changes in the brain related to the functional outcome in schizophrenia patients.

Study	Year	Subjects	Methods (intervals between scans)	Findings
Davis et al. (9)	1998	53 chronic patients (22 Kraepelinian and 31 non-Kraepelinian)	Longitudinal CT (mean intervals of 5 years)	The ventricles showed a bilateral increase in size over 4-year interval in the Kraepelinian subgroup, more marked in the left hemisphere than the right
Lieberman et al. (10)	2001	51 first-episode patients and 13 controls	Longitudinal MRI (at least 12 months)	Progressive ventricular enlargement in patients with poor outcome schizophrenia
Ho et al. (12)	2003	73 recent-onset patients and 23 controls	Longitudinal MRI (mean intervals of 3 years)	Patients with poor outcome had a greater lateral ventricular enlargement over time than patients with good outcome
Brickman et al. (13)	2004	106 chronic patients and 42 controls	MRI	Patients showed significantly smaller thalamic areas, and the effects were most marked in the patients with poor outcome
Mitelman et al. (14)	2005	37 chronic patients and 37 controls	MRI	Poor outcome subgroup exhibited significant bilateral gray matter deficits in posterior cingulate and retrosplenial cortices compared to good outcome patients
Cahn et al. (15)	2006	31 first-episode patients	Longitudinal MRI (1 year) and 5-year outcome	Progressive brain volume changes of gray matter during the first year of illness were significantly associated with clinical and functional outcome 5 years after the first episode
Mitelman et al. (16)	2006	104 chronic patients (51 good outcome and 53 poor outcome) and 41 controls	Diffusion tensor imaging	Overall white matter fractional anisotropy was reduced in patients with poor outcomes in both hemispheres
Wood et al. (17)	2006	46 patients with first-episode psychosis	Proton MRS	Low scores on the NAA/Cr ratio in the prefrontal cortex were related to poorer outcome
van Haren et al. (11)	2008	96 patients and 113 controls	Longitudinal MRI (over 5 years)	Poor outcome patients showed more brain tissue loss during the follow-up interval than good outcome patients
Wobrock et al. (18)	2009	45 first-episode patients	MRI, follow-up to 1 year	A significant reduced area of the left anterior limb of the internal capsule in patients with clinically relevant deterioration compared to those with stable psychopathology
Mitelman et al. (19)	2009	Chronic schizophrenia (26 poor outcome and 23 good outcome patients) and 16 controls	Longitudinal MRI (4 years)	The rate of decline in volumes of the putamen was greater in patients with poor outcome than in the good outcome group
Mitelman et al. (20)	2010	49 chronic patients and 16 controls	Longitudinal MRI (4 years)	Progressive enlargement of the posterior horn in the poor outcome (Kraepelinian) group
van Haren et al. (21)	2011	96 patients and 113 controls	Longitudinal MRI, vertex-by-vertex basis (5 years)	Frontal and temporal cortices showed excessive thinning over time, possibly related to outcome and medication intake
Tully et al. (22)	2014	26 patients and 29 controls	MRI, surface-based morphometry	Cognitive control fully mediated the relationship between cortical thickness in the superior frontal gyrus and role functioning
Dusi et al. (23)	2017	Chronic schizophrenia (35 poor outcome, 35 good outcome patients, and 76 controls)	Longitudinal MRI (3 years)	At baseline, poor outcome patients showed significantly decreased right dorsolateral prefrontal cortex (DLPFC) white matter volumes compared to controls, with shrinkage of left DLPFC white matter volumes at follow-up

Volume reduction in the insular cortex was noted in schizophrenia patients but not in schizotypal patients compared with healthy control subjects (35, 36). On longitudinal comparison, first-episode patients showed a significant gray matter reduction of the insular cortex over time compared with controls (37, 38). In chronic schizophrenia patients, however, no significant changes were found (38).

Thus, volume reductions in the superior temporal gyrus and insular cortex have been shown to progress during the first episode, but they may become stable in the chronic stage.

With regard to the prefrontal areas, schizophrenia patients showed reductions in the volume of the anterior cingulate gyrus, dorsolateral prefrontal areas (superior, middle, and inferior frontal gyri), and straight gyrus, while schizotypal patients had larger volumes of the bilateral middle frontal gyrus (26) or Brodmann area 10 (39) compared with healthy controls. Yamasue et al. (40) demonstrated that the effect size of volume reductions in schizophrenia patients was largest in the anterior cingulate gyrus among prefrontal and temporolimbic regions (superior temporal gyrus, amygdale–hippocampus complex, insula, and anterior cingulate gyrus).

In longitudinal studies, early schizophrenia patients showed a progressive reduction in the frontal lobe white matter volume, which was associated with more negative symptoms (12). A meta-analysis of 27 longitudinal volumetric studies (28) revealed that patients with schizophrenia showed significantly greater decreases over time in the frontal gray and white matter, parietal white matter, and temporal white matter volumes than healthy controls. Thus, frontal lobe alterations in schizophrenia may progress in patients, at least in part, through the first episode and chronic stage.

Slight but significant enlargement of the lateral ventricle, especially in the left hemisphere, is one of the most consistent morphological brain changes in schizophrenia patients (41, 42). This enlargement is most likely due to the volume reductions of the adjacent white matter of the brain. With regard to this, Suzuki et al. (43) and Zhou et al. (44) reported white matter reductions in the anterior limb of the internal capsule in schizophrenia patients. It is interesting to note that bidirectional glutamatergic fronto-thalamic fibers pass through the anterior limb of the internal capsule. In longitudinal studies on first-episode schizophrenia, it was found that poor outcome patients showed an increase in the ventricle volume over time, whereas the ventricle volume of good outcome patients and controls did not change (10). In chronic schizophrenia, progressive ventricle enlargement has also been reported in poor outcome patients (9, 11).

Voxel-Based Morphometry (VBM)

The VBM method has the advantage of being able to explore local morphological changes in the whole brain. Suzuki et al. (43) using voxel-based analysis, reported that the gray matter in schizophrenia patients was significantly reduced in the medial temporal, left superior temporal, left middle and inferior frontal, right inferior frontal, and bilateral anterior cingulate areas compared with healthy controls.

Kawasaki et al. (45) studied gray matter changes in schizophrenia and schizotypal disorder patients compared with healthy controls by VBM of three-dimensional MRI. They found that the volume of the medial temporal lobe structure and superior temporal gyrus was reduced in both schizophrenia and schizotypal disorder patients compared with healthy controls, whereas volume reductions in the frontal gyri were prominent only in schizophrenia patients.

Subsequent meta-analyses of VBM studies (46, 47) revealed gray matter reduction in a network of frontal, temporal, thalamic, and striatal regions in schizophrenia patients relative to healthy comparison subjects. Despite some discrepancies (48), these results are consistent with those using the region of interest method and support the view of Siever and Davis (49) and Kurachi (50) that frontal lobe alterations play a crucial role in the development of schizophrenia.

Honea et al. (51), using the VBM method, demonstrated that schizophrenia patients showed volume reductions in the bilateral superior and middle frontal gyri, left inferior frontal gyrus, and right thalamus compared with their unaffected siblings with no history. Furthermore, Hao et al. (52), using voxel-based analysis of diffusion tensor imaging, demonstrated that both schizophrenia patients and their healthy siblings showed reduced white matter fractional anisotropy in the left prefrontal cortex and hippocampus in comparison with healthy controls, while only schizophrenia patients exhibited reduced white matter fractional anisotropy in the left anterior cingulate cortex in comparison with both siblings and controls.

Thus, cross-sectional region of interest as well as VBM sMRI studies showed volume reductions in medial temporal lobe structures, peri-Sylvian regions, and prefrontal areas including fronto-thalamic connections in schizophrenia patients compared with healthy controls. Longitudinally, volume reduction in the peri-Sylvian regions (e.g., superior temporal gyrus and insula) progressed during the first episode, but became stable in the chronic stage. On the other hand, morphological changes in the frontal lobe and lateral ventricle progressed through the first episode and chronic stage.

CLINICAL CORRELATES OF MORPHOLOGICAL CHANGES IN SCHIZOPHRENIA AND A PATHOPHYSIOLOGICAL MODEL

Several studies have reported clinical correlates of morphological changes in schizophrenia patients. Auditory hallucinations have been reported to be associated with gray matter volume reductions in the left (anterior) superior temporal gyrus and Heschl's gyri by the region of interest method (30, 53) and a subsequent VBM study (54).

Shenton et al. (55) reported that the severity of formal thought disorder was negatively correlated with the volume of the left posterior superior temporal gyrus, and a VBM study (56) also showed the correlation with the gray matter volume reduction within the left temporal lobe in addition to the right middle orbital and cuneus/lingual gyri.

According to the study by Takahashi et al. (38), the gray matter loss of the left insular cortex over time in first-episode patients was correlated with the severity of positive and negative symptoms on follow-up.

Thus, the structural alterations in the peri-Sylvian regions (e.g., superior temporal gyrus and insula) were related to positive psychotic symptoms such as auditory hallucinations, thought disorder, and possibly delusions.

With regard to negative symptoms, a correlation with functional and structural alterations in prefrontal areas and the medial thalamus has been reported (12, 57). This correlation was clearly evidenced by a VBM study (58) although insular gray matter volume may also be involved in negative symptoms (59).

In addition to positive and negative symptoms, neurocognitive dysfunctions, especially executive dysfunctions, are an important aspect of schizophrenia, since they are related to the functional outcome (3). A meta-analysis of 41 functional neuroimaging studies of the executive function in schizophrenia patients (60) revealed that patients with schizophrenia showed reduced activity in the dorsolateral prefrontal cortex, anterior cingulate cortex, and mediodorsal nucleus of the thalamus. Consistent with this, a sMRI study showed that the executive dysfunctions were correlated with volume reduction in the bilateral dorsolateral prefrontal cortex in schizophrenia patients (61). Regarding memory impairment, deficits in memory organization have been shown to be a characteristic feature in schizophrenia patients (62). Memory organization deficits were related to volume reduction in the prefrontal cortex (63).

Studies on the morphological brain changes related to the functional outcome in schizophrenia patients are summarized in **Table 1**. First, in accordance with the report by Keefe et al. (64), which suggested morphological brain changes, e.g., ventricle enlargement, in the Kraepelinian (most severely deteriorated) chronic schizophrenic patients, progressive enlargement of the

lateral ventricle has been one of the most consistent findings in poor outcome patients (9–12). This enlargement is at least in part derived from the volume reduction of the anterior limb of the internal capsule, through which the bidirectional fronto-thalamic fibers pass. Volume reductions in the anterior limb of the internal capsule in schizophrenia patients were related to verbal and spatial memory (65) and the social outcome (18). Furthermore, a marked reduction in sleep spindles in schizophrenia patients also suggests impairment of the thalamo-frontal circuitry in this disease (66–68).

Second, prefrontal alterations were reported to be related to a poor outcome in schizophrenia patients (17, 22, 23). Notably, Tully et al. (22) reported that the relationship between the prefrontal alterations and poor outcome were mediated by impaired cognitive control (category fluency).

Third, other brain areas were also mentioned (11, 16, 21). van Haren et al. (21) reported progressive decreases in the cortical thickness in the superior temporal cortex as well as anterior cingulate cortex in patients with poor outcomes based on the vertex-by-vertex method. These findings appear to disagree with the results using the region of interest method (33, 34). In addition, the study by van Haren et al. is characterized by a large sample with a wide ranging duration of illness.

With regard to outcome measures, clinical criteria by Keefe et al. (64) have been frequently used as well as the Global Assessment of Functioning (GAF) score. In 2013, the American Psychiatric Association (69), instead of the GAF, adopted the WHO Disability Assessment Schedule (WHODAS 2.0) in Diagnostic and Statistical Manual of Mental Disorders-5.

To briefly summarize, volume reductions in the peri-Sylvian regions are mainly related to positive symptoms, whereas alterations in the regions composing the fronto-thalamic circuitry are mainly related to negative symptoms, executive functions, and the functional outcome. These two types may be called the peri-Sylvian type and fronto-thalamic type, respectively, and this model may provide a pathophysiological basis for Crow's (70) positive and negative syndrome classification (**Table 2**). Traditional simple type schizophrenia is a good example of the fronto-thalamic type, as evidenced by Suzuki et al. (71). This model could explain why positive psychotic symptoms are not significantly correlated with the functional outcome, since it proposes that positive psychotic symptoms and the functional outcome have distinct underlying pathophysiologies.

From the viewpoint of this pathophysiological model, it is noteworthy that the morphological brain changes in schizophrenia patients of discordant and concordant twins are not identical. According to a VBM study (72), patients with schizophrenia of discordant twins showed volume reductions in peri-Sylvian regions as well as the fronto-thalamic circuitry, whereas patients with schizophrenia of concordant twins showed volume reductions in the fronto-thalamic circuitry, but not in the peri-Sylvian regions.

TABLE 2 | Pathophysiological modeling of schizophrenia.

Type	Peri-Sylvian type	Fronto-thalamic type
Brain regions involved	Superior temporal gyrus, insula	Anterior cingulate gyrus Dorsolateral prefrontal gyrus Dorsomedial thalamus
Chemical pathology	Excessive DA neurotransmission	Imbalance in glutamate-GABA system
Clinical manifestations	Positive symptoms (delusions, hallucinations, disorganized speech)	Negative symptoms (diminished emotional expression, avolition) Executive dysfunctions Disability in social functioning
Clinical course	Progressive during the prodromal and first-episode stages, but stable in the chronic stage	Progressive both in the first episode and chronic stages
Responsiveness to treatment	Responsive	Refractory

DA, dopamine; GABA, gamma-aminobutyric acid.

EARLY INTERVENTION

Early intervention consists of two parts: one is early intervention in first-episode psychosis, and the other is that toward the prodromal phase. The main aim of early intervention in first-episode psychosis is to reduce the DUP. Hegelstad et al. (73) studied the effect of this reduction on the 10-year outcome. As a result, 30.7% of the patients from the early-detection area (a median DUP of 5 weeks) fulfilled recovery criteria, while only 15.1% of the patients from the usual-detection area (a median DUP of 16 weeks) did so. For the further improvement of the recovery rate, early intervention toward the prodromal phase would be required.

Since a prodrome is a retrospective concept, the term of "at-risk mental state (ARMS)" has been used in prospective trials (74). Early intervention for help-seeking individuals with ARMS will be necessary, since such subjects suffer the distress of symptoms and are liable to develop disability in functioning.

Importantly, in longitudinal studies, volume reductions in the planum temporale, caudal superior temporal gyrus, and insular cortex progressed in ultra-high-risk (UHR) subjects who later developed psychosis compared with controls or UHR subjects who did not develop it (32, 75). Hence, volume reductions in the peri-Sylvian regions (e.g., superior temporal gyrus and insula) have been shown to progress during the prodromal phase.

The transition risk from ARMS to psychosis was 29–36% over a 2- to 3-year follow-up (76). This figure is markedly higher than the incidence rate of psychosis in the general population, but it should be noted that two-thirds of subjects were false positive using these ARMS criteria.

Thus, for an indicated early intervention, it is necessary to diagnose those who are truly in the prodromal phase among ARMS patients. Effective examination would detect the subclinical pathophysiological process. In accordance with this, several candidate biomarkers have been reported, such as the neurocognitive function, event-related potential, and sMRI. In addition, the Minnesota Multiphasic Personality Inventory may be a useful tool to assess the risk of transition to psychosis.

The cognitive function is impaired in ARMS patients as well as in first-episode and chronic schizophrenia patients (6). In particular, the verbal memory and executive functions of ARMS

subjects who later developed psychosis were reported to be lower than in those who did not develop psychosis (77–79). Notably, ARMS patients who developed psychosis or did not show remission during the 2-year follow-up showed a similar impairment in the global cognitive function at the baseline to that in first-episode psychosis patients (79). In addition, the disease transition was predicted by multivariate pattern recognition of the neurocognitive performance (78).

Mismatch negativity (MNN) is a component of event-related potentials that reflects preattentive auditory sensory memory. MMN amplitudes are likely to provide an index of *N*-methyl-D-aspartate (NMDA) receptor-mediated neurotransmissions (80–82). It has been reported that converters to psychosis elicit a reduced amplitude of duration MMN (dMMN), i.e., MMN in response to duration deviants, relative to non-converters (83–85). Hence, it may be possible to use dMMN to predict the conversion from ARMS to psychosis (86, 87).

Concerning the morphological changes in the brain, Koutsouleris et al. (88) revealed that ARMS patients with subsequent disease transition showed prefrontal alterations relative to those in ARMS patients without subsequent disease transition and healthy controls. Subsequently, Koutsouleris et al. (78) showed that the early prediction of psychosis may be reliably enhanced using neuroanatomical pattern recognition at the single-subject level.

A systematic review and meta-analysis (89) demonstrated decreased prefrontal, cingulate, insular, and cerebellar gray matter volumes in high-risk subjects with subsequent transition to psychosis compared with high-risk subjects without transition. In particular, the thickness of the anterior cingulate gyrus was significantly reduced in individuals with ARMS who later developed psychosis relative to healthy subjects (47, 90, 91). These findings, together with those by Yamasue et al. (40) and Hao et al. (52), described in the previous section, suggest the crucial role of the anterior cingulate gyrus in the emergence of schizophrenic symptoms, in which self-disturbance might be fundamental (92, 93).

With regard to the dorsolateral frontal cortex, Reniers et al. (94) reported that lower baseline gray matter densities in the middle and inferior frontal gyri were significantly correlated with a decline in the GAF score over the follow-up, regardless of the transition status or persistence of ARMS. These findings along with the Kopelowicz et al.'s report (5) that frontal lobe functioning (executive function, verbal fluency, and verbal working memory) was associated with recovery from schizophrenia suggest the significance of the prefrontal lobe in social functioning and recovery from this condition.

Minnesota Multiphasic Personality Inventory, consisting of 550 questionnaires, is an established tool to assess personality and psychopathology (95). In our experience in the early intervention project, high scores on Scale 8 (schizophrenia) were associated with subsequent transition to psychosis (96). Subtle alterations of subjective experience may precede changes in objective measures as stated by Klosterkötter et al. (97) and Parnas and Handest (98).

Concerning the early intervention trials including antipsychotic medication or psychological intervention for ARMS patients, a meta-analysis of randomized controlled trials revealed that the overall risk of transition to psychosis was reduced by 54% at the 12-month follow-up (99). In view of the report that cognitive remediation improved memory and psychosocial functioning in first-episode psychiatric outpatients (100) and functional connectivity in early-course schizophrenia patients (101), cognitive remediation may also be effective for ARMS patients.

Whether early intervention in the prodromal phase significantly improves the long-term recovery rate of schizophrenia patients remains elusive. To answer this question, follow-up studies of ARMS patients who subsequently developed psychosis are needed.

In the next section, potential candidate compounds are described, capable of ameliorating the subclinical pathophysiological process, particularly, the histological brain changes in schizophrenia patients.

A DIRECTION OF NOVEL THERAPEUTICS

The understanding of the disease is composed of three levels: symptomatic, pathophysiological, and etiological. Therapeutics have been developed corresponding to these three levels. Current pharmacotherapy for schizophrenia remains at the symptomatic level, and so the long-term recovery rate has not changed, as described in the previous session. Owing to the recent development of technologies in neuroscience, our understanding of the pathophysiological disease process of schizophrenia has markedly progressed.

Olney and Farber (102) proposed that NMDA receptor hypofunction was a key mechanism that can help explain major clinical and pathophysiological aspects of schizophrenia, including the occurrence of structural brain changes, and stated that NMDA receptor hypofunction on GABAegic neurons would reduce inhibitory control over multiple downstream neurons.

Garey et al. (103). and Glantz and Lewis (104) reported a reduced dendritic spine density on pyramidal neurons in layer of the prefrontal and temporal cortex in postmortem brains of schizophrenia patients, and this was considered to explain the loss of cortical volume without the loss of neurons under this condition.

Furthermore, Reynolds et al. (105) and Zhang and Reynolds (106) reported a loss of parvalbumin–immunoreactive interneurons in the dorsolateral prefrontal cortex and hippocampus in schizophrenia patients. Chung et al. (107) demonstrated that the excitatory synapse density is selectively lower on parvalbumin interneurons in schizophrenia patients and that this may lead to the alterations of cortical gamma oscillations and working memory dysfunction.

Thus, a reduced dendritic spine density on pyramidal neurons and a loss of parvalbumin–immunoreactive interneurons in the cerebral cortex may be core features of histological changes in the brain of schizophrenia patients.

Importantly, animal models of schizophrenia, constructed on the basis of the NMDA receptor hypofunction hypothesis, successfully mimic these histological changes in the brain of schizophrenia.

Nakatani-Pawlak et al. (108) reported that mice neonatally treated with phencyclidine showed impairments of spatial working memory and social interaction behavior in adulthood, in

addition to decreases in the number of parvalbumin-positive cells and spine density in the frontal cortex, nucleus accumbens, and hippocampus. Uehara et al. (109, 110) also reported augmented MAP-induced hyperlocomotion, sensorimotor gating deficits, and a loss of GABAergic parvalbumin-positive neurons in rats neonatally exposed to MK-801, an antagonist of the NMDA receptor.

Thus, utilizing these rodent animal models, it became possible to explore or develop novel therapeutics to improve cognitive deficits and the histological changes in the brain of schizophrenia patients.

There may be at least two approaches to develop novel therapeutics. One is to stimulate the glycine/D-serine modulatory site on the NMDA receptor with glycine (111) or D-serine (112). Another strategy is to explore medicines that ameliorate dysfunctional GABAergic neurons. The latter strategy is based on the concept that the hypofunction of NMDA receptors located on GABAergic neurons leads to the attenuated activity of GABAergic neurons, and this, in turn, produces abnormal gamma oscillations and cognitive deficits in schizophrenia patients (113).

Based on these lines, several candidate compounds have been reported. First, the ketamine-induced loss of parvalbumin-positive interneurons has been reported by an increase in brain superoxide due to the activation of NADPH oxidase in neurons (114). Subsequently, Zhang et al. (115) reported that apocynin, an inhibitor of NADPH oxidase, attenuated the cognitive impairments and downregulation of parvalbumin and glutamic acid decarboxylase 67 in rats after repeated ketamine exposure during the neonatal period.

Second, Shirai et al. (116) reported that the antioxidant sulforaphane, found in cruciferous vegetables, significantly attenuated hyperlocomotion and the prepulse inhibition deficits in mice after phencyclidine administration. Furthermore, the dietary intake of sulforaphane-rich broccoli sprout extracts attenuated cognitive deficits and the decrease in parvalbumin-positive cells in the medial prefrontal cortex and hippocampus of these mice (117).

Third, Uehara et al. (110, 118) found that T-817MA, a novel neurotrophic agent, restores parvalbumin-positive GABAergic neurons in the prefrontal cortex and hippocampus of the rat models described above. Haloperidol and risperidone showed no such effect. T-817MA is a newly synthesized agent that was developed for the treatment of neurodegenerative disorders, such as Alzheimer's disease, and it is markedly protective against Aβ-induced or H_2O_2-induced neuronal death (119).

Furthermore, Nakamura et al. (120) reported that the oral administration of T-817MA ameliorated behavioral, histological, and neurophysiological changes, such as deficits in prepulse inhibition, reduced levels of parvalbumin-immunoreactive neurons in the medial prefrontal cortex, hippocampus, and amygdala, and a deficit in the auditory phase-locked gamma oscillation in a mouse model of schizophrenia. The modulation of gamma band activity is noteworthy, because abnormal gamma band activity is thought to underlie the psychosis and cognitive deficits, and is considered a target for potential therapeutic interventions (113).

These compounds have antioxidant effects in common (114, 116, 119). In accordance with this, the antioxidant *N*-acetyl cysteine was reported to prevent the reduction of prefrontal parvalbumin interneuron activity as well as electrophysiological and behavioral deficits in the animal models of schizophrenia (121).

Considering that the dysfunction of parvalbumin-positive GABAergic neurons by NMDA receptor antagonists was mediated by oxidative mechanisms (114), some antioxidants might be novel therapeutics or lead compounds to ameliorate the cognitive deficits and histological disease process in schizophrenia patients.

CONCLUSION

Structural neuroimaging studies on schizophrenia revealed that volume reductions in the peri-Sylvian regions are mainly related to positive symptoms, whereas alterations in the fronto-thalamic regions are mainly related to negative symptoms, executive functions, and the functional outcome. These two types, i.e., the peri-Sylvian type and fronto-thalamic type, may provide a pathophysiological basis for Crow's (70) positive and negative syndrome classification. This model may explain why positive psychotic symptoms are not significantly correlated with the functional outcome, since it proposes that positive psychotic symptoms and functional outcomes are associated with distinct pathophysiology.

Accumulated evidence from early intervention trials suggests that the transition rate to psychosis is approximately 30% among individuals with ARMS. Differences in the cognitive performance, MNN, and brain morphology have been reported between ARMS patients who later develop psychosis and those who do not. The prefrontal lobe function may have a significant role in social functioning and recovery from schizophrenia. Whether early intervention for ARMS significantly improves the long-term recovery rate of schizophrenia patients remains elusive.

With respect to the development of novel therapeutics, animal models of schizophrenia based on the *N*-methyl-D-aspartate receptor hypofunction hypothesis showed histological changes in the brain that successfully mimicked those in the postmortem brains of schizophrenia patients, i.e., decreased numbers of parvalbumin-positive interneurons and dendritic spines of pyramidal neurons in the frontal cortex, in addition to behavioral abnormalities associated with cognitive impairment. Some antioxidant compounds, e.g., apocynin, sulforaphane, and T-817MA, have been found to ameliorate histological changes in the brain and cognitive dysfunction in these animal models.

In conclusion, early intervention coupled with novel therapeutics, herein reviewed, may provide a promising strategy to substantially improve the functional outcome of schizophrenia patients. However, further studies are needed to evaluate the functional outcome in relation to these therapeutic strategies, which is beyond the scope of this review.

AUTHOR CONTRIBUTIONS

MK wrote the first draft of the manuscript. TT, TS, TU, and MS contributed to the cited studies and discussed the content of this manuscript.

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Semantic Memory Organization in Japanese Patients With Schizophrenia Examined With Category Fluency

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Background: Disorganization of semantic memory in patients with schizophrenia has been studied by referring to their category fluency performance. Recently, data-mining techniques such as singular value decomposition (SVD) analysis have been reported to be effective in elucidating the latent semantic memory structure in patients with schizophrenia. The aim of this study is to investigate semantic memory organization in patients with schizophrenia using a novel method based on data-mining approach.

Method: Category fluency data were collected from 181 patients with schizophrenia and 335 healthy controls at the Department of Psychiatry, Osaka University. The 20 most frequently reported animals were chosen for SVD analysis. In the two-dimensional (2D) solution, item vectors (i.e., animal names) were plotted in the 2D space of each group. In the six-dimensional (6D) solution, inter-item similarities (i.e., cosines) were calculated among items. Cosine charts were also created for the six most frequent items to show the similarities to other animal items.

Results: In the 2D spatial representation, the six most frequent items were grouped in the same clusters (i.e., *dog, cat* as pet cluster, *lion, tiger* as wild/carnivorous cluster, and *elephant, giraffe* as wild/herbivorous cluster) for patients and healthy adults. As for 6D spatial cosines, the correlations (Pearson's *r*) between 17 items commonly generated in the two groups were moderately high. However, cosine charts created for the three pairs from the six most frequent animals (*dog–cat*, *lion–tiger*, *elephant–giraffe*) showed that pairwise similarities between other animals were less salient in patients with schizophrenia.

Discussion: Semantic memory organization in patients with schizophrenia, revealed by SVD analysis, did not appear to be seriously impaired in the 2D space representation, maintaining a clustering structure similar to that in healthy controls for common animals. However, the coherence of those animals was less salient in 6D space, lacking pairwise similarities to other members of the animal category. These results suggests subtle but structural differences between the two groups. A data-mining approach by means of SVD analysis seems to be effective in evaluating semantic memory in patients with schizophrenia, providing both a visual representation and an objective measure of the structural alterations.

Keywords: schizophrenia, cognition, semantic memory, category fluency, singular value decomposition analysis

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INTRODUCTION

Cognitive impairment in patients with schizophrenia is a cardinal feature of the disease and is generally independent of positive or negative psychiatric symptoms (e.g., hallucinations or withdrawal). This impairment disturbs favorable functional outcomes of patients, including daily living skills, social functioning, and work (1–4). Accordingly, comprehensive cognitive batteries have been developed to assess the cognitive function of patients with schizophrenia. Currently, the Brief Assessment of Cognition in Schizophrenia (BACS) (5) and MATRICS Consensus Cognitive Battery (MCCB) (6) are the most acknowledged batteries, and they have been used for research and clinical purposes.

Although those "gold-standard" cognitive batteries have been reported to be effective for predicting functional outcomes in patients with schizophrenia (7), the target domains are mainly executive aspects of cognition (i.e., attention, processing speed, and visual/verbal working memory). Higher order cognition, such as semantic memory, has received less attention, although disorganization of semantic memory has been considered as one of the intermediate cognitive phenotypes in patients with schizophrenia (8).

The paucity of studies seems to be largely due to the lack of powerful tools, such as the MCCB or BACS. For healthy subjects, cognitive experiments (e.g., semantic priming) have been frequently used to estimate the latent structure of semantic memory. However, an experimental setting is often too demanding for patients with mental disorders that attenuate attention or motivation.

Alternative methods have been developed to assess semantic memory in patients with schizophrenia. The aim of this study was to investigate semantic memory organization in patients with schizophrenia introducing a novel method based on data-mining approach. Earlier attempts in this line of research were also briefly reviewed.

PREVIOUS APPROACH FOR ASSESSING SEMANTIC MEMORY IN PATIENTS WITH PSYCHIATRIC DISORDERS

Less demanding methods, compared to experimental settings, have been explored for evaluating semantic memory organization in patients with schizophrenia. Most of them utilized verbal outputs in the category fluency task (CFT), partly because the CFT is included in established cognitive batteries (e.g., the MCCB and BACS), and also because the task is simple both for testers and subjects. The CFT is a free recall task, asking a subject to produce as many items in a given category (e.g., animal) as possible in a designated time (typically 1 min).

There are two lines of research on the methods for estimating semantic structures using the CFT. They differ in terms of measurement of similarities; one uses on "adjacency" while another uses "co-occurrence" of outputs in the CFT.

The earlier approach focus on adjacency of the words produced in the CFT, assuming that it reflects semantic associations in memory. In some studies, specific formulas were modeled to convert the word order to dissimilarities (9–11) for submission to advanced statistical analyses to visualize the structures [e.g., multidimensional scaling (MDS) or hierarchical cluster analysis (HCA) (**Figure 1**)]. In another technique, cluster indices

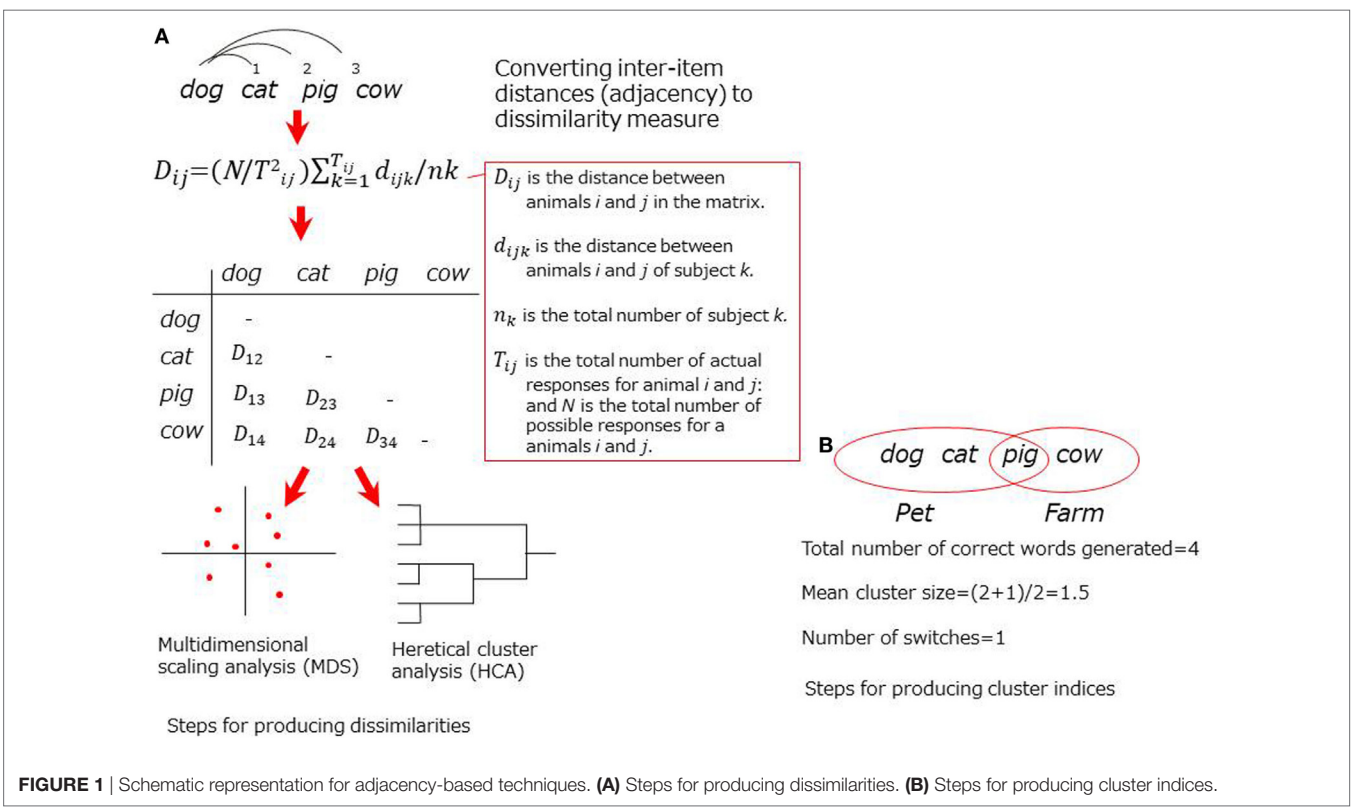

FIGURE 1 | Schematic representation for adjacency-based techniques. **(A)** Steps for producing dissimilarities. **(B)** Steps for producing cluster indices.

(i.e., a cluster size or a switching score) are designated based on predefined clustering rules (12). Studies using either technique have successfully demonstrated aberrant structurers of semantic memory in patients with schizophrenia (10, 12–15).

Critical limitations for adjacency-based approach, as noted above, have been addressed. In studies using formulas for dissimilarities, the results were likely to be inaccurate if the sample size was small (16, 17). In studies using cluster indices, scoring tended to be arbitrary because the predefined clustering rules (e.g., farm animals, pet) were somewhat intuitive. In addition, the clustering rules may not be universal across cultures (e.g., *pig* was listed in a pet cluster, but it may not be true in other countries like Japan).

NEW APPROACH TO ESTIMATE SEMANTIC MEMORY

Recently, data-mining techniques, such as singular value decomposition (SVD), have been applied to the CFT to examine the deeper structure of semantic memory (18–20). SVD is a general matrix factorization technique based on eigenvalue decomposition [**Figure 2**; for further information, see supplementary materials in Ref. (18–20)].

One notable difference between the data-mining approach and adjacency-based techniques is the basic measurement with "co-occurrence" of items across the participants rather than "adjacency," the latter of which has been used in previous techniques. For example, in the earlier techniques, *dog* and *cat* show higher proximity in a *dog*, *cat*, *pig* sequence than *dog*, *pig*, *cat*. In the new technique, the proximity would be the same as long as *dog* and *cat* are produced in a sequence of word outputs (i.e., "co-occur") by a subject.

A strength of SVD analysis is that inter-item similarities can be estimated even if no subjects produce a particular pair (i.e., *dog–snake*), which can occur in small samples. Mathematical simplicity and clarity are also superior in SVD analysis. This established mathematical method has been used in many scientific fields, including genetics (21) as well as applied linguistics (22). In contrast, in adjacency-based techniques (9–11), formulas are presented to general high-end users without sufficient information for modeling.

Singular value decomposition analysis has already been applied to the CFT performance of patients with schizophrenia. Sung et al. (18) demonstrated subtle differences between patients with schizophrenia and healthy adults by looking at higher dimensional structures of semantic memory, which may not have been elucidated in studies using the previous techniques. In brief, patients with schizophrenia showed similar semantic clustering in the lower dimensional SVD solution, but it was less coherent in the higher dimensional solution, suggesting that semantic deterioration occurred in the latent structure.

PRELIMINARY STUDY

Given a positive result from a previous study using SVD analysis (18), we aimed to investigate semantic structures in Japanese patients with schizophrenia by applying SVD analysis to the CFT. In particular, we were interested in whether this novel method could also be useful to show structural differences in semantic memory between Japanese patients with schizophrenia and healthy adults as has been reported in previous studies (18).

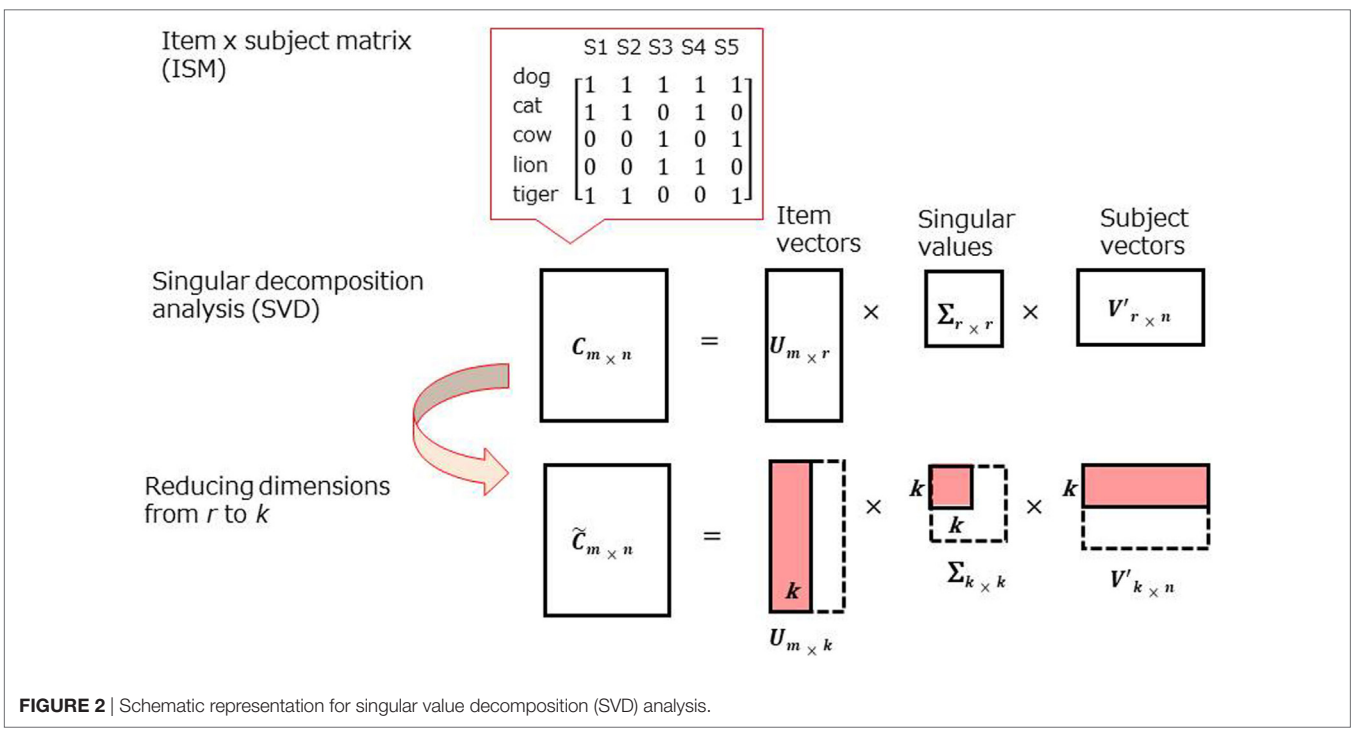

FIGURE 2 | Schematic representation for singular value decomposition (SVD) analysis.

Participants

Data were collected from 181 patients with schizophrenia and 335 healthy controls at the Department of Psychiatry, Osaka University. **Table 1** presents the characteristics of the participants. All patients met the DSM-IV criteria for schizophrenia (23). The diagnosis was made by experienced psychiatrists based on the Structured Clinical Interview for DSM-IV (SCID) for schizophrenia. Healthy controls were recruited from the community through local advertisements at Osaka University. All participants provided written informed consents. The study protocol was approved by the Ethical Committee of Osaka University, and the procedures were conducted according to the Declaration of Helsinki.

Assessment

Verbal Fluency Tasks

The CFT and letter fluency task (LFT) were administered following the normative method (24). In the CFT, an animal was used as a cue, while three hiragana letters ("*fu*," "*a*," and "*ni*") were used in the LFT. Subjects were asked to produce as many animal names (CFT) or words beginning with a specified letter (LFT) as possible in one minute. The CFT score represented the total outputs for animal category, while the LFT score represented the mean of outputs for three letters. Errors [i.e., repetitions, proper nouns, and intrusions (e.g., *apple* for an animal cue)] were excluded from outputs.

Intelligence

Current intelligence (full-scale intelligence quotient, FIQ) was assessed by the Japanese version of the Wechsler Memory Scale-Third edition (WAIS-3) (25) as part of a larger neuropsychological assessment (26–30). The third edition was used because the fourth edition has not yet been released in Japan. Premorbid intelligence was estimated by the Japanese version of the Adult Reading Test (JART) (31). This test is composed of 50 Japanese kanjis (ideographic scripts), and the reading task is considered to be equivalent to irregular word reading employed in the National Adult Reading Test (31–33).

Psychiatric Symptoms

The patients were assessed with the Positive and Negative Syndrome Scales (34) to evaluate psychiatric symptoms. The evaluation was made following the five-factor model of the scale (i.e., positive, negative, cognition, excitement, and depression/anxiety) (35, 36).

Analysis

Characteristics of Participants

Male-female ratio was tested by x^2 test. Other demographic characteristics (age and years of education), IQ measures (FIQ and JART), and verbal fluency measures (CFT score and LFT score) were compared between patients and healthy controls using *t*-tests. In addition, effects sizes (Hedges's *g*) were calculated for relevant variables. The statistical significance was set at $p < 0.05$ (two-tailed) in all analyses. SPSS ver. 22.0 was used for statistical analyses.

SVD Analysis

As noted in Assessment section, rule breaks (i.e., repetitions, intrusions, and proper nouns) were removed from the analysis. An item × subject matrix (ISM) was created for the patient group and healthy adult group (two matrices in total). Rows of the ISM

TABLE 1 | Characteristics of participants.

	HC	SCZ	x^2/t	*df*	*p*	*g*[e]
N[a]	335 (154/181)	181 (107/74)	8.12[b]	1	0.004	
Age	35.80 (11.90)	36.76 (12.16)	–0.87	514	0.383	–0.08
Education (years)	15.20 (2.20)	14.20 (2.49)	4.40	514	<0.0001	0.19
Duration (years)	–	12.66 (10.46)	–	–	–	–
Onset	–	24.10 (8.80)	–	–	–	–
Neuroleptics (mg)[c]	–	182.65 (365.76)	–	–	–	–
PANSS positive	–	14.79 (4.93)	–	–	–	–
Negative	–	17.48 (6.35)	–	–	–	–
Cognition	–	11.87 (4.12)	–	–	–	–
Excitement	–	8.23 (3.22)	–	–	–	–
Depression/anxiety	–	9.88 (3.53)	–	–	–	–
Full IQ	108.67 (12.28)	86.93 (17.56)	15.68	479	<0.0001	1.55
Performance IQ	109.31 (12.15)	91.76 (16.94)	11.98	437	<0.0001	1.21
Verbal IQ	107.13 (13.11)	83.53 (17.08)	16.60	437	<0.0001	1.56
Premorbid IQ (JART)	107.09 (8.02)	101.48 (10.17)	6.88	514	<0.0001	0.51
LFT score[d]	10. 07 (2.96)	7.43 (2.75)	9.90	514	<0.0001	0.91
CFT score	20.94 (4.51)	15.86 (4.67)	12.06	514	<0.0001	0.69

HC, healthy controls; SCZ, patients with schizophrenia; PANSS, The positive and negative syndrome scale; JART, Japanese Adult Reading Test; LFT, Letter fluency task; CFT, Category fluency task.

Male/female and SD are presented in parentheses.

[a]*Several variables had missing values. Degree of freedom varied accordingly.*

[b]*Chi-squared test.*

[c]*CPZ equivalent.*

[d]*The mean of the three letters.*

[e]*Hedges's g (effect size).*

contained animal items (e.g., *dog*, *cat*, etc.), while columns contained subjects, and each cell contained a co-occurrence of items (**Figure 2**, top). Each row (i.e., item) is treated as a vector in the space produced by SVD. Due to technical limitations in creating large-scaled ISMs, 20 of the most frequently reported animals in each group were chosen for SVD analysis (**Table 2**, above the line).

Item vectors in reduced dimensions were used to produce a visual representation and inter-item similarities. For visual interpretation, item vectors were plotted on the two-dimensional (2D) space, while inter-item similarities were calculated in a higher dimensional space. In SVD analysis, inter-item similarities were presented by the cosines between item vectors in SVD analysis, but not the Euclidian distance between items as presented in the MDS analysis. Accordingly, a cosine close to 1.0 indicates that two items are highly similar (two words frequently co-occur across subjects), while −1.0 implies that they are most dissimilar (two words are produced independently).

TABLE 2 | Frequency ranks of animal items.

Rank	HC (N = 335)	Frequency	SCZ (N = 181)	Frequency
1	Dog	309	Dog	169
2	Cat	305	Cat	163
3	Lion	250	Lion	143
4	Giraffe	244	Elephant	119
5	Tiger	239	Giraffe	119
6	Elephant	235	Tiger	116
7	Monkey	234	Monkey	106
8	Horse	171	Cow	74
9	Sheep	163	Horse	74
10	Cow	155	Mouse	69
11	Mouse	152	Rabbit	64
12	Rabbit	148	Hippopotamus	63
13	Hippopotamus	143	Bird	62
14	Bear	122	Sheep	62
15	Rhinoceros	116	Pig	55
16	Bird	115	Bear	53
17	Panda	110	Leopard	49
18	Cheetah	102	Deer	46
19	Snake	102	Snake	43
20	Zebra	102	Zebra	40
21	Wildboar	101	Rhinoceros	39
22	Gorilla	96	Panda	37
23	Leopard	95	Wildboar	36
24	Whale	92	Fox	35
25	Koala	87	Cheater	32
26	Dolphin	83	Seaotter	32
27	Penguin	83	Whale	32
28	Chimpanzee	77	Goat	29
29	Deer	76	Squirrel	29
30	Orangutan	71	Dolphin	28
31	Pig	69	Raccoondog	28
32	Goat	68	Gorilla	27
33	Racoondog	68	Chimpanzee	25
34	Fox	67	Crocodile	25
35	Hen	65	Koala	25
36	Kangaroo	65	Hen	24
37	Sparrow	61	Penguin	24
38	Crocodile	56	Sparrow	24
39	Camel	52	Pigeon	23
40	Seaotter	52	Crow	21

HC, healthy controls, SCZ, patients with schizophrenia.
The most frequent 20 items were submitted to singular value decomposition analyses.

R ver. 3.2.2 (37) and its LSA package (38) were used for conducting SVD analysis and producing inter-item cosines.

Results

Group Comparisons

Table 1 presents results from group comparisons. The verbal fluency performance was significantly better in healthy controls than patients with schizophrenia (LFT score: $t = 9.90$, df = 514, $p < 0.001$, CFT: $t = 12.06$, df = 514, $p < 0.001$). The same trend was found in intelligence measures (FIQ: $t = 15.68$, df = 479, $p < 0.001$, VIQ: $t = 11.98$, df = 437, $p < 0.001$ PIQ: $t = 16.60$, df = 437, $p < 0.001$, premorbid IQ: $t = 6.88$, df = 514, $p < 0.001$). Age did not significantly differ between the two groups ($t = -0.87$, df = 514, $p = 0.38$). Patients had less education than healthy adults ($t = 4.40$, df = 514, $p = 0.001$) although the difference was small as was indicate by the minor effect size ($g = 0.19$).

SVD Analysis

As previous studies have suggested (39), there is no statistical rules for choosing an appropriate number of singular values (dimensions) for the dimensionality reduction. Therefore, the number was determined at the point at which a fraction of the sum of the selected singular values to the sum of all singular values reached 0.5. A six-dimensional solution (6D) satisfied the criterion, and therefore, inter-item cosines were calculated in this dimension. As noted earlier, a 2D solution was also produced in which item vectors were plotted on the 2D space.

Two-Dimensional Space Representations

Figure 3 presents the plots of the most frequently produced 20 items (**Table 2**) on 2D space. Dimensions 2 and 3 were used because the first dimension in SVD solutions is generally determined by the frequencies of items in the whole dataset, and it is not informative for showing semantic associations (18). Overall, the most frequent six items were grouped in the same clusters between patients and healthy adults: *dog, cat* as a pet cluster, *lion, tiger* as a wild/carnivorous cluster, and *elephant, giraffe* as a wild/herbivorous cluster (**Figures 3A,B**, circled items).

Cosines in Six-Dimensional Space

Table 3 shows the inter-item cosines of the 20 most frequent items in healthy adults (**Table 3A**) and patients (**Table 3B**). Cosine values were all positive probably because only the 20 most frequent items were used. Due to high frequency, those items necessarily co-occurred with each other; therefore, the cosine values tended to be non-negative. Similar trends were found in a previous study [see **Figure 2** in Ref. (18)], where cosines of highly frequent items (e.g., cat) yielded almost all positive values to other items. In that study, negative values appeared as the item became less frequent (e.g., whale).

Of all the 20 items, 17 items were in common between healthy adults and patients (i.e., *bear, bird, cat, cow, dog, elephant, giraffe, hippopotamus, horse, lion, monkey, mouse, rabbit, sheep, snake*, and *tiger*). Thus, the correlation (Pearson's r) was calculated using those items to examine whether the cosine values were similar between the two groups. The correlation was moderately high ($r = 0.78$, $p < 0.01$), suggesting that a pattern of inter-item

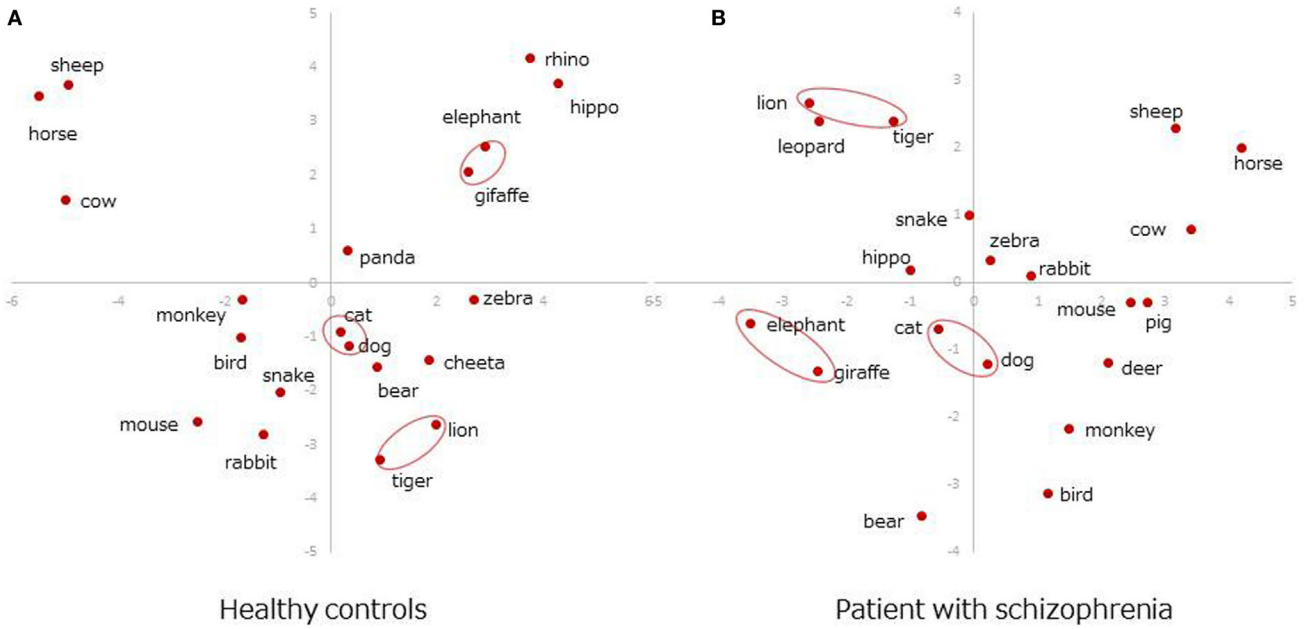

FIGURE 3 | Two-dimensional space representations. **(A)** Healthy controls. **(B)** Patient with schizophrenia.

similarities between frequent items in patients with schizophrenia is comparable to that in healthy adults.

To further examine structural similarities (or differences) between the two groups, cosine charts (**Figures 4A,B**) were created for the six most frequent animals (i.e., d*og, cat, lion, tiger, elephant,* and *giraffe*). The lines represent 6D cosine values between a particular animal (e.g., *dog*) and the other most frequent 20 items. Overall, cosine values fluctuated more in patients than in healthy controls. In healthy controls, the patterns of line charts were highly similar between *dog–cat* pair (red, pet items) and the rest of the items. Similar trends were also found for the *lion–tiger* pair (blue, wild/carnivorous items) and *elephant–giraffe* pair (green, wild/herbivorous items) (**Figure 4A**). However, those pair-wise similarities were less salient in patients with schizophrenia, except for the *dog–cat* pair (**Figure 4B**).

DISCUSSION

We, first, reviewed the methods to evaluate semantic memory organization in patients with schizophrenia. Then, we reported the study that investigated the semantic memory structure in Japanese patients with schizophrenia by applying a newly developed data-mining technique (i.e., SVD analysis) to their category fluency data.

Semantic memory organization in patients with schizophrenia did not appear to be seriously disorganized in the 2D space representation, maintaining a similar clustering structure to that in healthy controls for highly frequent animals. However, the coherence of those animals was less salient in the 6D space, lacking pair-wise similarities to other members of the animal category. This result suggested that subtle but structural differences existed between the two groups.

Evaluation of SVD Analysis

Although highly frequent animals were clustered in a similar manner in 2D space in patients with schizophrenia and heathy adults, the coherence of those items became weaker in 6D space in the patient group. The animal pair in the same cluster (i.e., d*og–cat, lion–tiger, elephant–giraffe*) yielded almost the same cosine values to the rest of items in healthy adults (**Figure 4A**). This pair-wise trend was less salient in patients with schizophrenia, except the *dog–cat* pair (**Figure 4B**). As suggested by a previous study (18), this result indicates that SVD analysis can reveal subtler structural differences in semantic memory between patients and healthy controls than are revealed by MDS or HCA.

Our results confirmed the findings from a previous study using English-speaking patients with schizophrenia (18). Thus, newly developed techniques based on a data-mining approach, such as SVD analysis, seems to be effective for elucidating the latent structure of semantic memory in patients with schizophrenia.

Limitations

Several limitations of this study should be noted. First, we had to limit the number of items (i.e., the 20 most frequent items) due to technical reasons in creating ISM using our R program. If less frequent items were included, further differences, as reported in previous studies (18, 19), might have been observed.

Second, we did not address the issue of possible reasons for poor CFT performance in patients with schizophrenia. Some authors assume that this is due to an impoverished semantic structure (10, 40), while others explain the deterioration based on impairment of accessibility to category items (41–43).

TABLE 3 | Cosines in six-dimensional space for the most frequent 20 items.

A. Healthy controls

	Bear	Bird	Cat	Cow	Dog	Elephant	Giraffe	Hippopotamus	Horse	Lion	Monkey	Mouse	Rabbit	Sheep	Snake	Tiger	Zebra	Cheetah	Rhinoceros
Bear	0.47	0.71	0.58	0.71	0.69	0.79	0.51	0.55	0.70	0.56	0.59	0.62	0.43	0.56	0.71	0.52	0.33	0.39	0.95
Bird		0.78	0.55	0.79	0.56	0.58	0.52	0.64	0.69	0.82	0.49	0.37	0.67	0.82	0.67	0.32	0.58	0.41	0.49
Cat			0.80	1.00	0.93	0.93	0.80	0.80	0.96	0.96	0.84	0.75	0.81	0.76	0.95	0.81	0.72	0.73	0.67
Cow				0.79	0.75	0.74	0.49	0.97	0.74	0.78	0.87	0.65	0.94	0.46	0.77	0.56	0.50	0.47	0.62
Dog					0.92	0.93	0.80	0.79	0.96	0.96	0.83	0.74	0.80	0.77	0.95	0.80	0.72	0.72	0.67
Elephant						0.98	0.92	0.75	0.91	0.85	0.76	0.70	0.75	0.56	0.88	0.90	0.66	0.89	0.68
Giraffe							0.89	0.75	0.89	0.85	0.74	0.75	0.73	0.64	0.86	0.85	0.57	0.84	0.76
Hippopotamus								0.56	0.75	0.75	0.46	0.49	0.61	0.52	0.69	0.80	0.57	0.98	0.52
Horse									0.69	0.81	0.76	0.58	0.98	0.52	0.70	0.49	0.44	0.54	0.63
Lion										0.88	0.86	0.68	0.69	0.62	0.99	0.87	0.84	0.68	0.65
Monkey											0.80	0.76	0.85	0.83	0.87	0.72	0.63	0.69	0.50
Mouse												0.83	0.75	0.53	0.90	0.77	0.63	0.43	0.49
Rabbit													0.56	0.72	0.71	0.70	0.25	0.42	0.42
Sheep														0.54	0.70	0.52	0.49	0.60	0.51
Snake															0.61	0.40	0.27	0.38	0.42
Tiger																0.85	0.83	0.62	0.64
Zebra																	0.72	0.80	0.42
Cheetah																		0.56	0.35
Rhinoceros																			0.43

B. Patients with schizophrenia

	Bear	Bird	Cat	Cow	Dog	Elephant	Giraffe	Hippopotamus	Horse	Lion	Monkey	Mouse	Rabbit	Sheep	Snake	Tiger	Zebra	Deer	Leopard
Bear	0.58	0.62	0.25	0.62	0.49	0.59	0.55	0.31	0.54	0.80	0.53	0.49	0.29	0.19	0.53	0.33	0.62	0.37	0.09
Bird		0.59	0.66	0.66	0.59	0.51	0.12	0.35	0.57	0.71	0.63	0.51	0.27	0.58	0.61	0.58	0.66	0.26	0.69
Cat			0.75	0.99	0.91	0.97	0.76	0.73	0.86	0.85	0.68	0.71	0.72	0.82	0.85	0.91	0.76	0.68	0.66
Cow				0.80	0.63	0.61	0.46	0.80	0.63	0.64	0.86	0.80	0.75	0.77	0.69	0.90	0.70	0.45	0.88
Dog					0.91	0.95	0.71	0.74	0.86	0.88	0.72	0.73	0.71	0.84	0.85	0.92	0.80	0.64	0.72
Elephant						0.96	0.68	0.44	0.84	0.66	0.54	0.64	0.42	0.84	0.81	0.88	0.50	0.74	0.61
Giraffe							0.76	0.56	0.81	0.76	0.53	0.61	0.55	0.79	0.77	0.85	0.64	0.65	0.58
Hippopotamus								0.46	0.58	0.48	0.65	0.79	0.48	0.38	0.56	0.69	0.34	0.69	0.17
Horse									0.62	0.75	0.64	0.54	0.99	0.67	0.66	0.69	0.84	0.38	0.67
Lion										0.79	0.58	0.59	0.64	0.85	0.99	0.77	0.60	0.87	0.50
Monkey											0.63	0.53	0.72	0.66	0.80	0.64	0.93	0.46	0.57
Mouse												0.96	0.59	0.47	0.66	0.77	0.59	0.53	0.55
Rabbit													0.51	0.47	0.65	0.81	0.44	0.64	0.47
Sheep														0.66	0.67	0.66	0.79	0.43	0.59
Snake															0.85	0.86	0.61	0.65	0.81
Tiger																0.78	0.61	0.87	0.53
Zebra																	0.60	0.66	0.80
Deer																		0.19	0.70
Leopard																			0.19

Items in gray columns are presented as line charts in ***Figure 4.***

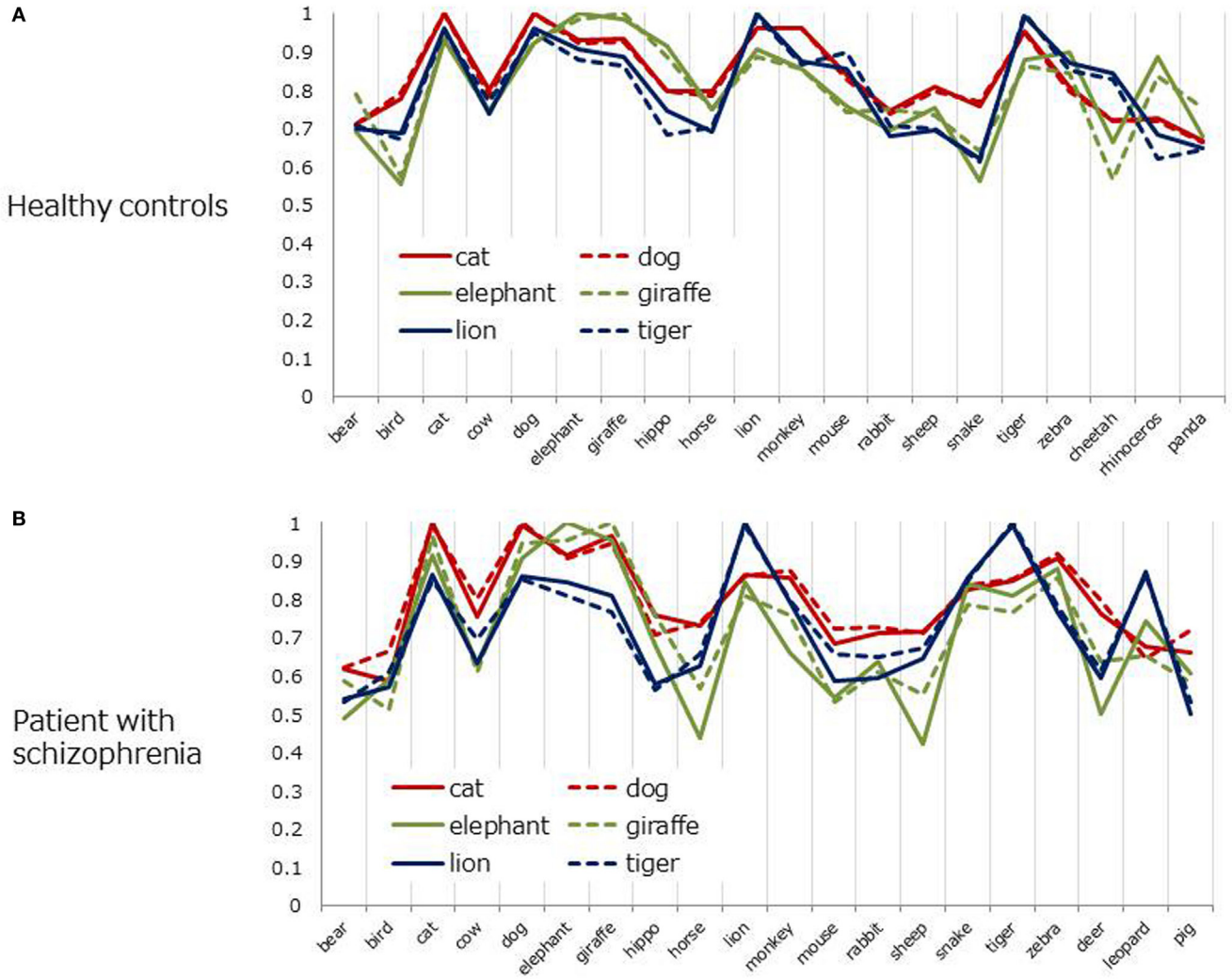

FIGURE 4 | Cosine values between six frequent animals and other items (six-dimensional space). **(A)** Healthy controls. **(B)** Patient with schizophrenia.

Although previous studies using SVD analysis took the latter view (18, 19), we are not certain whether semantic structure derived from SVD analysis, in which co-occurrence of items is the basic measurement, could support either the former or the latter view.

CONCLUSION

The current study investigated the semantic structure of patients with schizophrenia and healthy adults by applying SVD analysis to their category fluency data. A data-mining approach, such as SVD analysis, seems to be effective for evaluating semantic memory in patients with schizophrenia, providing both a visual representation (e.g., 2D spatial representation) and an objective measure (e.g., cosine values) of the structural differences compared to healthy adults. Future studies should aim to address the mechanism of poor performance on the CFT in patients with schizophrenia, as well as the methodological problems surrounding the assessment for the deficits in semantic memory.

ETHICS STATEMENT

The Ethical Committee of Osaka University. All participants provided written informed consents. The study protocol was approved by the Ethical Committee of Osaka University, and the procedures were conducted according to the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

CS designed the study, under the supervision of RH and TS. HF, HY, MF, and YY collected the data. CS conducted the analyses and wrote the initial draft. TS, FH, and RH critically revised the draft for important intellectual content. All authors contributed to the manuscript writing.

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Neuropsychological Profile of Specific Executive Dysfunctions in Patients with Deficit and Non-deficit Schizophrenia

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Objectives: Although it has been shown that there are more profound deficits present in deficit schizophrenia (DS) patients than in non-deficit schizophrenia (NDS) patients, there still remain some matters requiring further investigation. In this context, we formulated three research aims: (1) to compare executive functions between the investigated groups, (2) to determine the relationship between particular aspects of executive functions within the groups, and (3) to draw up a neuropsychological profile for executive functions.

Methods: The study involved 148 schizophrenia patients divided into two groups on the basis of the Schedule for the Deficit Syndrome: DS ($n = 70$) and NDS ($n = 78$). Patients were matched for sex, age, years of education, and overall cognitive functioning. For assessing executive functions we used the Wisconsin Card Sorting Test (WCST), the Trail Making Test (TMT), the Phonemic Verbal Fluency Test (VFT P), the Stroop Color and Word Test (SCWT), and the Go/No Go task (GNG).

Results: Deficit schizophrenia patients scored lower on the WCST and TMT (relative flexibility) than did the NDS patients. There were no inter-group differences in the VFT P, SCWT (relative inhibition), or GNG. There were significant correlations between WCST and TMT scores in both groups. The general neuropsychological profiles were similar in both groups.

Conclusion: Deficit schizophrenia patients exhibited slightly greater interference with concept formation and non-verbal cognitive flexibility. Therefore, such problems may be specific to this particular type of schizophrenia. These results may be useful for the development of neuropsychological diagnostic methods for patients with schizophrenia.

Keywords: executive functions, concept formation, verbal cognitive flexibility, non-verbal cognitive flexibility, deficit schizophrenia

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INTRODUCTION

There is an ongoing discussion about whether different types of schizophrenia are associated with specific types of executive dysfunction (Brazo et al., 2002; Simon et al., 2009; Fioravanti et al., 2012; Hegde et al., 2013; Ventura et al., 2013). The heterogeneity of schizophrenia symptoms has led to a distinction between different clinical syndromes within a single disease. The term

'deficit schizophrenia' was first suggested by Carpenter et al. (1988) as a type of schizophrenia with dominant negative symptoms persisting for a long time. Among these are persistent and primary negative symptoms such as social withdrawal, poverty of speech, limited content of verbal expression, apathy, and blunting of affect (Strauss et al., 2010). Longitudinal analyses show that these symptoms are stable over time (Tek et al., 2001; Chemerinski et al., 2006; Strauss et al., 2010). There are numerous reports confirming the validity of deficit schizophrenia (DS) diagnoses (Tek et al., 2001; Arango et al., 2004; Messias et al., 2004; Dickerson et al., 2006; Cohen et al., 2007; Galderisi et al., 2008; Kirkpatrick and Galderisi, 2008; Pełka-Wysiecka et al., 2013). However, apart from negative/deficit symptoms, the basic symptomatic dimensions in schizophrenia include also reality distortion and disorganization (Liddle et al., 1992; Schröder et al., 1992). The occurrence of the two latter types of symptoms may also be associated with executive function impairments.

The construct of executive functions has enabled a more insightful understanding of the self-regulatory processes responsible for the management of one's thoughts, emotions, and behavior (Alvarez and Emory, 2006; Jurado and Rosselli, 2007; Diamond, 2013). In clinical neuropsychology, it has been assumed that they form a superordinate system which allows the implementation of purposeful action, and involves four domains: volition, planning, purposive action, and effective performance (Lezak, 1995; Jodzio, 2008). Many clinical and experimental studies have confirmed that these functions are carried out by a complex central executive network which includes a variety of brain structures, the most important of which are the prefrontal cortex, the anterior cingulate cortex, the subcortical nuclei, and the cerebellum (Stuss, 2011; Niendam et al., 2012; Yuan and Raz, 2014; Mak et al., 2016). Many studies suggest the presence of greater structural and functional disorders of the brain in DS patients than in their NDS counterparts (Liddle et al., 1992; Tamminga et al., 1992; DeQuardo et al., 1998; Heckers et al., 1999; Lahti et al., 2001). Based on these studies, Buchanan et al. (1994) and Kirkpatrick et al. (2001) asserted that malfunctioning of the loop created by the prefrontal cortex, the inferior parietal cortices, and the thalamus is implicated in the pathophysiology and executive dysfunctions of the deficit syndrome in schizophrenia.

As can be seen in **Table 1**, neuropsychological analyses of the executive functioning of patients with DS and non-deficit schizophrenia (NDS) yield somewhat inconsistent results. Polgár et al. (2010) showed that patients with DS achieved lower scores than those with NDS in specific measures of the Wisconsin Card Sorting Test (WCST). In addition, a factor analysis was performed, showing that there are at least two factors relating to mental processes engaged in this test. The first is concept formation and flexibility, and it includes, inter alia, Perseverative Responses (PR), and Perseverative Errors (PE). The second is unsuccessful problem-solving with an ineffective hypothesis-testing strategy and includes Non-perseverative Errors (NPE). Analysis of the results showed that only some DS patients obtained lower PE scores than did those with NDS (**Table 1**). Other reports found no inter-group differences (or differences in PR score, see **Table 1**). These particular scores are not considered at all in some papers. Furthermore, Wang et al. (2008) and Vogel et al. (2013) report some contradictory findings, as their subjects differed in terms of PE scores, but not PR scores. NPE scores were only considered in four papers, and only Réthelyi et al. (2012) found that patients with DS had lower scores than those with NDS. A review of research which used the Trail Making Test (TMT, version B) revealed that, in some papers, patients with DS scored lower than NDS patients. Unfortunately, only two papers reported patient scores for absolute non-verbal cognitive flexibility [time B – A], some independent of the speed of information processing (TMT AF, Chan et al., 2015). In the study of Wang et al. (2008), patients with DS obtained lower scores than those with NDS, while Galderisi et al. (2002) did not report any inter-group differences. A meta-analysis of research which used the Phonemic Verbal Fluency Test (VFT P) to measure verbal cognitive flexibility showed that DS patients scored lower than NDS patients in three studies, while in five others there were no reports of any inter-group differences. A review of studies which used the Stroop Color and Word Test (SCWT) showed that only in the study by Réthelyi et al. (2012) did DS patients score lower than NDS patients in the task of reading the names of colors printed in a color different (incongruent) to that denoted by the name. Cohen et al. (2007) found no inter-group differences. Buchanan et al. (1994) was the only study in which the interference index was applied, where reaction time was controlled for the congruent trial. The authors showed that DS patients exhibited higher (worse) scores than did the NDS patients. We could not find any available research on DS patients performing the Go/No Go task (GNG).

Furthermore, the specific relationship between the particular aspects of DS and NDS may prove important for understanding the nature of executive functions in DS/NDS patients, as demonstrated in research conducted on healthy persons (Miyake et al., 2000) and older subjects (McCabe et al., 2010; Brown et al., 2012). Unfortunately, such relationships have been very rarely examined in this group of patients. Only Yu et al. (2015) managed to demonstrate a significant correlation between scores on the TMT and VFT P in patients with DS. It may also be important to identify which aspects of executive function are most impaired in patients with DS and NDS. This is made possible by a profile analysis of neuropsychological function (Lezak et al., 2004; Voglmaier et al., 2005). Brazo et al. (2002) found the greatest disturbance in patients with DS in areas of concept formation (Modified Card Sorting Test, MCST) and verbal cognitive flexibility (VFT P), and their non-verbal cognitive flexibility (TMT) and cognitive inhibition (SCWT) were least affected. The aforementioned functions remained on a similar level in NDS patients. In turn, Cascella et al. (2008) demonstrated that DS patients exhibit the greatest difficulty with speed of information processing and verbal cognitive flexibility (VFT P), and they tend to do slightly better in concept formation (MCST), with a similar profile observed in both DS and NDS patients. However, Réthelyi et al. (2012) and Yu et al. (2015) showed that patients with

TABLE 1 | Survey of studies on PubMed which test executive functions in deficit schizophrenia (DS) and non-deficit schizophrenia (NDS) patients, and normal controls (CON).

Authors	Number of DS/NDS/CON	WCST			TMT		VFT P	SCWT	
		WCST PR/%	WCST PE/%	WCST NPE/%	TMA B	TMT AF		SCWT I	SCWT AI
Buchanan et al., 1994	18/21/30[a,b,c]	ns	ni	ni	<0.05	ni	ns	ni	ni
Bryson et al., 2001	33/57/none[a,b,c]	ni	<0.05	ni	ni	ni	ni	ni	ni
Galderisi et al., 2002	58/54/26[a,b,c]	ni	ns	ni	ni	ns	ni	ni	ni
Horan and Blanchard, 2003	15/30/41[a,c]	ni	<0.05	ni	ni	ni	ni	ni	ni
Tiryaki et al., 2003	19/43/none[a,b,c]	ni	ni	ni	ns	ni	ns	ns	ni
Delamillieure et al., 2004	5/17/21[a,b,c]	ni	ni	ni	ni	ni	ni	ns	ni
Cohen et al., 2007	20/25/25[a,b,c]	ni	ns	ni	ns	ni	ns	ni	ns
Cascella et al., 2008	26/79/316[a,b,c]	ni	ns	ni	ns	ni	ns	ni	ni
Polgár et al., 2008	27/45/30[a,b,c]	ni	<0.05	ni	<0.05	ni	<0.05	ni	ni
Wang et al., 2008	30/93/103[a,b,c]	ns	<0.05	ns	<0.01	<0.01	ni	ni	ni
Polgár et al., 2010	154/121/130[a,b,c]	<0.05	<0.05	<0.05	ni	ni	ni	ni	ni
Réthelyi et al., 2012	143/123/none[a,b]	ni	<0.001	<0.001	<0.001	ni	<0.001	<0.001	ni
Vogel et al., 2013	15/52/51[a,b,c]	ns	<0.01	ns	ni	ni	ni	ni	ni
Csukly et al., 2014	30/28/29[a,b,c]	ni	<0.001	ni	ni	ni	ni	ns	ni
Scala et al., 2014	15/40/55[a,b,c,d]	ns	ns	ns	ni	ni	ns	ni	ni
Yu et al., 2015	40/57/52[b]	ni	ni	ni	<0.001	ni	<0.05	ns	ni

ni, no information; ns, no significant; WCST, Wisconsin Card Sorting Test; PR, Perseverative Responses; PE, Perseverative Errors; NPE, Non-perseverative Errors; TMT, Trail Making Test; B, time; AF, Absolute Flexibility [time B – A]; VFT P, Phonemic Verbal Fluency Test; SCWT, Stroop Color and Word Test: I, Incongruent; AI, Absolute Inhibition [time incongruent – congruent].

[a] *Deficit schizophrenia and non-deficit schizophrenia and normal controls matched for gender.*

[b] *Age.*

[c] *Years of education.*

[d] *Premorbid intelligence quotient.*

DS and NDS have greater problems with regards to non-verbal flexibility (TMT), than with verbal cognitive flexibility (VFT P).

As can be seen in the above results, there are still a few unresolved issues concerning executive function in patients with DS. First of all, the precise nature of executive dysfunction in this group of patients has not been established. Secondly, it is not clear what is the relationship between various aspects of the executive function in those patients or whether there exists any at all. Also, it is not fully known which domains of the described processes suffer the greatest impairment within the group. Therefore, both the inconclusiveness of findings and the importance of executive functions for the performance of complex actions have led to formulation of three research aims: (1) to compare executive function performance between the investigated groups, (2) to determine the relationship between the particular aspects of executive functions within the groups, and (3) to draw up a neuropsychological profile for executive functions which takes into account the diversity of the different aspects of these processes.

MATERIALS AND METHODS

Participants

The patient group consisted of 148 right-handed Caucasians (74 female and 74 male) who had been diagnosed with schizophrenia according to ICD-10 (World Health Organization [WHO], 1992) for a minimum of 18 months. Patient interviews were done by properly licensed psychiatrists. Among the inclusion criteria were the ability to understand the research procedure, being aged between 20 and 60, and having given informed consent. Exclusion criteria were other mental diseases, neurological diseases, dementia, a history of traumatic brain injury, and severe diseases of the parenchymal organs, a history of alcohol or drug misuse, or intellectual disability. With the construction of the study in mind, patients who exhibited clear symptoms of disorganization were also excluded. The patients were recruited from inpatient psychiatric wards, psychiatric daycare wards, and outpatient clinics in the Western Pomerania district of Poland. All subjects were fully informed about the aims and the protocol of the study and all gave written informed consent. The protocol was approved by the local bioethics committee.

Measures

Clinical Assessment

The presence of psychopathological symptoms was assessed using the Positive and Negative Syndrome Scale (PANSS, Kay et al., 1987), and the Clinical Global Impression – Schizophrenia scale (CGI-SCH, Haro et al., 2003), which assessed four groups of symptoms (positive, negative, depressive, and cognitive) during a psychiatric examination. To describe the severity and type of deficit symptoms, we used a Polish translation of the Schedule for the Deficit Syndrome (SDS, Kirkpatrick et al., 1989). DS was diagnosed by the presence of the following negative symptoms:

restricted affect, diminished emotional range, poverty of speech, curbing of interests, diminished sense of purpose, and diminished social drive. All the above symptoms had to be primary, i.e., not caused by positive symptoms such as depression, cognitive dysfunction, psychopharmacotherapy, or poor general health, and had to have been present for the preceding 12 months.

The patients were in symptomatic remission, not acute psychosis. All subjects were treated according to the guidelines for the psychopharmacological treatment of schizophrenia. In both groups the patients received typical (perazine, zuclopenthixol, haloperidol) or atypical (risperidone, olanzapine, clozapine, quetiapine, aripiprazole, amisulpride) antipsychotics. The DS and NDS groups did not differ in terms of type of neuroleptics used.

Neuropsychological Assessment

In this study we used the WCST in its original computerized form (Heaton et al., 1993; Jaworowska, 2002). Based on data collected by Polgár et al. (2010), we decided to measure concept formation using two scores: PE and PR, and to assess problem-solving using NPE. The subject's task was to discover the rule that is currently in place (color, shape or number) and answer by pressing the right key on the keyboard, from 1 to 4 based on the feedback (correct or incorrect) displayed on a 15″ screen. Before the test, each participant received instructions from a psychologist. For the assessment of non-verbal cognitive flexibility, we used the TMT (Reitan, 1958). However, bearing in mind that DS and NDS patients' speed of information processing is generally slower (Morrens et al., 2007), we decided to use the Relative Flexibility indicator (TMT), applying the formula: $\left[\left(\text{time B} - \text{A}/\text{time B}\right) \times 100\right]$ (Stuss et al., 2001; Perianez et al., 2007). In TMT A, subjects had to connect 25 circles containing numbers from 1 to 25, which were irregularly placed on a white, A4 sheet, with a continuous line, as quickly as possible. TMT B consisted of connecting circles, going by turns from number to letter, while preserving the order of numbers and following alphabet (from 1 to A, from A to 2, etc.), finishing at number "13" and the letter "L." A practice trial was done before each task so that the investigator could be sure that the patient understood the instructions. Instructions were provided verbally by the investigator (psychologist) both before the practice task and the actual task. In turn, to assess verbal cognitive flexibility, we administered the VFT P (Lezak, 1995; Tyburski et al., 2015). Each individual was asked to list as many words as they can, as fast as possible, according to the given criterion (words beginning with k or p). The time for completing each trial was 60 s. The researcher wrote down each word on an answer sheet. Since it has been demonstrated that the number of correctly spoken words strongly correlates with the number of word switches, this indicator was considered to be a good measure of verbal cognitive flexibility (Ross, 2003). We also assessed cognitive inhibition (dominant verbal response) by means of the SCWT. However, because patients with DS exhibit slowing of information processing (Morrens et al., 2007), we decided to use the Relative Inhibition Indicator (SCWT RI) in the formula: $\left[\left(\text{time incongruent} - \text{congruent}/\text{time congruent}\right) \times 100\right]$ (Denney and Lynch, 2009). In the first task, the subject had to read aloud as fast as possible the names of colors printed in a black font on a white A4 sheet. In the second task, the subject had to name the colors of words printed in a colored font, where the font color was incongruent with the word's meaning (e.g., the word "green" printed in red). Instructions were provided verbally each time by the investigator (psychologist) before the task. The computer version of the GNG was also used and motor inhibition was measured with the number of No Go type errors (Strauss et al., 2006; Wright et al., 2014). The subject's task was to press the spacebar on the keyboard when a green square appeared on the computer screen (15″), and to refrain from pressing the spacebar when a blue square appeared on the screen. Instructions were presented on the computer screen before the task.

Procedure

At their first appointment, all patients were examined by one of four psychiatrists who carried out a structured interview and assessment based on clinical scales (each patient was evaluated using the PANSS, CGI-SCH, and SDS). The psychiatrists were members of the research team and had been trained in the research procedure, including the use of the psychiatric scales. The next appointment involved neuropsychological assessment, carried out by one of three trained psychologists. All patients were examined with the same neuropsychological battery. Administration of each tool was preceded by the standard instructions.

Statistical Analysis

Statistical analysis of the results was done using the IBM SPSS 21 Statistical package. Continuous variables were presented as means (*M*) and standard deviations (*SD*) or standard errors (*SE*). The normality of the distribution was tested with the Shapiro–Wilk test. Before any analyses were conducted, square root transformation was used to transform the raw results of variables which were not normally distributed. Then selected scores were transformed into unitarized results using the formula $x_u = [(x_i - \min)/(\max - \min) \times 100]$ (ranges from 0 to 100, the higher the score, the more difficult the task). To check for differences between the groups, the non-parametric Mann–Whitney *U*-test (for demographic and clinical variables) or parametric Student's *t*-tests were used (for neuropsychological variables). The Wendt r_U rank-biserial correlation method (Wendt, 1972; Rosenthal and Rubin, 2003) was used to determine the magnitude of effect size measures for the non-parametric tests and Cohen's *d* or η^2 effect size (Cohen, 1992) was used to determine the magnitude of effect size measures for the parametric test and analysis of variance (ANOVA). For multiple comparisons the Bonferroni correction was used. To assess the strength of the relationship between different aspects of executive functioning, Pearson's *r* correlation coefficient was used. To draw up the executive function profile and compare the results from different neuropsychological tests, we used a repeated measures/mixed model ANOVA. We assumed the group type (DS or NDS) as the inter-object factor, and the aspect of executive function (the type of measure) as an intra-object 7-level factor scale.

RESULTS

Subjects' Characteristics

The patients' socio-demographic and clinical characteristics are shown in **Table 2**. Neither investigated group differed in terms of number of years of education, gender, length of time since diagnosis, level of general mental functioning (assessed with MMSE), or number of hospitalizations at psychiatric wards. DS patients had higher scores than non-deficit patients on all PANSS ($p < 0.001$) and SGI-SCH subscales ($p < 0.001$). The effect size (r_U) was found to be 0.25–0.74, i.e., a small to large effect size.

Performance in Specific Aspects of Executive Functions

As shown in **Table 3**, DS patients scored lower in concept formation (WCST PR: $p < 0.05$; WCST PE: $p < 0.05$) and non-verbal cognitive flexibility (TMT RF: $p < 0.05$) in comparison to NDS patients. The effect size (d) of executive dysfunctions in WCST and TMT was found to be 0.38–0.39, indicating a small effect size. No differences were observed in verbal cognitive flexibility (VFT P) and cognitive (SCWT RI) or motor inhibition (GNG).

Associations between Particular Aspects of Executive Functions

As can be seen in **Table 4**, there was a strong positive correlation between the two measures relating to concept formation (WCST PR and PE) in both groups, as well as a weak positive correlation between measures relating to concept formation (WCST PR and PE) and problem-solving (WCST NPE), and a small positive correlation between measures of concept formation (WCST PR and PE) and non-verbal cognitive flexibility (VFT P), as well as problem-solving and cognitive inhibition (SCWT RI). In addition, DS patients showed a slight positive correlation between measures relating to concept formation (WCST PR and PE) and cognitive inhibition (SCWT IR), as well as non-verbal (TMT RI) and verbal cognitive flexibility (VFT P). In turn, in patients with NDS, there was a positive correlation between measures relating to concept formation (WCST PR and PE), problem-solving (WCST NPE), and verbal cognitive flexibility (VFT P).

Neuropsychological Profile of Executive Functions

Figure 1 shows the profile of executive functions for both patient groups. ANOVA with repeated measures/mixed model showed significant differences between the different aspects of executive function in both patient groups [$F(6,608) = 57.41$; $p = 0.000$; $\eta^2 = 2.82$]. There was no statistically significant interaction effect between group type and the nature of the executive domain [$F(6,6.08) = 2.28$; $p = 0.057$; $\eta^2 = 0.02$]. Patients with DS ($M = 42.87$; $SE = 1.43$) had higher general scores than patients with NDS, which indicates more severe problems in terms of executive function [$F(1,146) = 4.30$; $p = 0.040$; $\eta^2 = 0.03$]. Pairwise comparison showed that patients with DS scored highest, indicating their greatest difficulties, in the VFT P ($M = 60.88$; $SE = 2.23$), and scored lowest in the GNG ($M = 29.56$; $SE = 2.80$), WCST NPE ($M = 37.90$; $SE = 2.25$), WCST PR ($M = 37.31$; $SE = 2.74$) and WCST EP ($M = 39.39$; $SE = 2.80$). It was similar in patients with NDS – the greatest problems occurred in the performance of VFT P ($M = 63.16$; $SE = 2.11$), and the least problematic were the WCST PR ($M = 28.48$; $SE = 2.59$), GNG ($M = 30.02$; $SE = 2.66$), WCST EP ($M = 30.46$; $SE = 2.6$), and WCST NPE ($M = 33.46$; $SE = 2.13$). In addition, patients with DS had similar results in TMT ($M = 50.48$; $SE = 2.16$) and SCWT RI ($M = 44.57$; $SE = 1.90$), which still differed significantly from the results obtained in the other measures. Patients with NDS also had similar results in TMT RF ($M = 43.72$; $SE = 2.05$) and SCWT RI ($M = 42.28$; $SE = 1.80$), which were also significantly different from the results in the other factors.

DISCUSSION

The results partially confirmed the first hypothesis. It was found that DS patients had lower levels of concept formation than did patients with NDS. Other researchers report similar findings (**Table 1**). However, in most studies there were only differences in the WCST in the PE score. Only Polgár et al. (2010) report that patients with DS both gave more PR and committed more PE than did NDS patients. Therefore, patients with DS are more likely to have diminished ability to use positive and negative feedback in the learning process and to react optimally to new situations. However, differences in the performance of this test between patients from the two groups could be due to decreased working memory efficiency (working memory is important for holding information in temporary storage, manipulating it, and using it to guide subsequent behavior), which has been noted by, e.g., Park and Gooding (2014). In addition, we have demonstrated that patients with DS have lower levels of non-verbal cognitive flexibility than do NDS patients. However, it was difficult to relate our results to the findings of other researchers, as they did not assess patients' performance on the TMT (Relative Flexibility Indicator). Wang et al. (2008) found a significant difference between DS/NDS patients regarding their scores on the Absolute Flexibility task, but Galderisi et al. (2002) did not report such a difference. In some studies (**Table 1**), patients with DS had longer response times in this task (part B), but these results should be interpreted with great caution, as there is a strong dependence between this measure and speed of processing information.

There were no inter-group differences in terms of verbal cognitive flexibility, or cognitive or motor inhibition. Admittedly, there are several studies in which patients with DS got lower results in the VFT P (Polgár et al., 2008; Réthelyi et al., 2012; Yu et al., 2015), but other researchers report no inter-group differences (**Table 1**). To interpret these results it may be important to note that the ability to generate words is of a complex nature and requires the use of many mental processes, not only set shifting, but also language competence, psychomotor speed, as well as episodic, semantic, and working memory (Szepietowska and Gawda, 2011). Furthermore, its neural correlates include various cooperating brain regions (Amunts et al., 2004). Therefore, the extent to which this task may

TABLE 2 | Demographic and clinical characteristics of deficit schizophrenia (DS) and non-deficit schizophrenia (NDS) patients.

	DS ($n = 70$)	NDS ($n = 78$)	Z/χ^2	p
Age (years): *M* (*SD*)	40.94 (9.95)	39.17 (11.24)	−1.07[a]	0.284
Education (years): *M* (*SD*)	12.23 (2.55)	12.88 (2.77)	−1.42[a]	0.156
Sex: male/female	38/32	36/42	0.68[b]	0.410
Relationship: yes/no	22/48	25/53	0.00[b]	1.000
Duration of illness (years): *M* (*SD*)	13.79 (7.08)	12.14 (8.10)	−1.82[a]	0.068
Number of hospitalizations: *M* (*SD*)	7.54 (6.18)	6.55 (5.61)	−1.10[a]	0.270
PANSS P: *M* (*SD*)	6.11 (4.35)	4.86 (5.41)	−2.58[a]	0.010
PANSS N: *M* (*SD*)	15.67 (5.97)	6.55 (5.47)	−7.80[a]	0.000
PANSS G: *M* (*SD*)	18.19 (8.75)	9.99 (8.45)	−5.52[a]	0.000
CGI-SCH: *M* (*SD*)	3.17 (1.09)	1.97 (0.91)	−6.38[a]	0.000
MMSE: *M* (*SD*)	28.23 (1.48)	28.46 (1.74)	−1.50[a]	0.137

PANSS, Positive and Negative Syndrome Scale; P, Positive; N, Negative; G, General; CGI-SCH, Clinical Global Impression – Schizophrenia; MMSE, Mini Mental State Examination.
[a]*Mann–Whitney U-test.*
[b]*Chi-square test.*

TABLE 3 | Comparison of raw scores of executive performance for deficit schizophrenia (DS) versus non-deficit schizophrenia (NDS) patients.

Aspects of executive functions	Tests and index	DS ($n = 70$) *M* (*SD*)	NDS ($n = 78$) *M* (*SD*)	t	p	d	Effect size
Concept formation	WCST PR	37.31 (23.58)	28.48 (22.26)	2.35	0.020	0.39	Small
	WCST PE	39.39 (24.16)	30.46 (22.66)	2.32	0.022	0.38	Small
Problem-solving	WCST NPE	37.90 (20.99)	33.46 (16.17)	1.43	0.154	–	None
Non-verbal cognitive flexibility	TMT RF	50.48 (18.41)	43.72 (17.83)	2.27	0.025	0.38	Small
Verbal cognitive flexibility	VFT P	60.88 (19.98)	63.16 (17.42)	−0.74	0.461	–	None
Cognitive inhibition	SCWT RI	44.57 (17.18)	42.28 (13.91)	−0.88	0.382	–	None
Motor inhibition	GNG NGE	29.56 (24.83)	30.02 (22.14)	−0.12	0.905	–	None

WCST, Wisconsin Card Sorting Test; PR, Perseverative Responses; PE, Perseverative Errors; NPE, Non-perseverative Errors; TMT, Trail Making Test: RF, Relative Flexibility [(time B - A/time B-A/time A)× 100]; VFT P, Phonemic Verbal Fluency Test; SCWT, Stroop Color and Word Test; RI, Relative Inhibition [(time incongruent - congruent/time congruent)× 100]; GNG NGE, Go/No Go Task, No Go Errors.

TABLE 4 | Correlation (Pearsons') between particular aspects of executive function for deficits schizophrenia (DS) and non-deficits schizophrenia (NDS) patients.

		Group	Concept formation	Problem -solving	Non-verbal cognitive flexibility	Verbal cognitive flexibility	Cognitive inhibition	Motor inhibition
			WCST PE	WCST NPE	TMT RF	VFT P	SCWT RI	GNG NGE
Concept formation	WCST PR	DS	0.99**	0.26**	0.34**	0.18	0.25*	0.06
		NDS	0.99**	0.40**	0.28*	0.36**	0.17	0.09
	WCST PE	DS		0.31**	0.35**	0.17	0.25*	0.06
		NDS		0.44**	0.29*	0.39**	0.17	0.10
Problem-solving	WCST NPE	DS			0.24*	0.09	0.25*	0.17
		NDS			−0.02	0.42**	0.28*	0.09
Non-verbal cognitive flexibility	TMT FR	DS				0.27*	0.10	0.17
		NDS				0.02	0.18	−0.04
Verbal cognitive flexibility	VFT P	DS					−0.02	0.06
		NDS					0.18	0.08
Cognitive inhibition	SCWT RI	DS						0.22
		NDS						*0.01*

*WCST, Wisconsin Card Sorting Test; PR, Perseverative Responses; PE, Perseverative Errors; NPE, Non-perseverative Errors; TMT, Trail Making Test; RF, Relative Flexibility [(time B - A/time A)× 100]; VFT P, Phonemic Verbal Fluency Test; SCWT, Stroop Color-Word Test; RI, Relative Inhibition [(time incongruent - congruent/time congruent)× 100]; GNG NGE, Go/No Go Task, No Go Errors. *$p < 0.05$, **$p < 0.01$.*

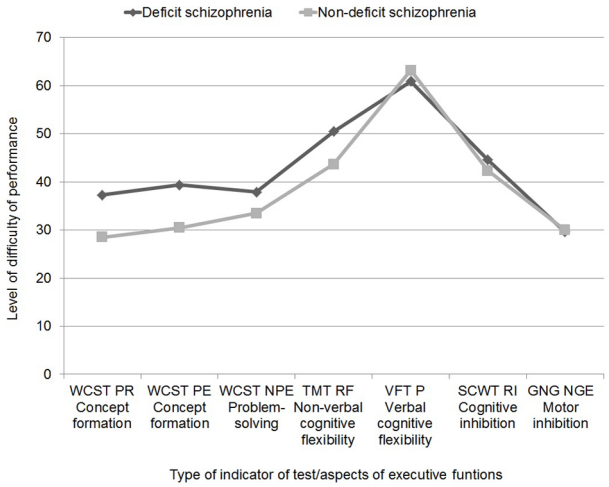

FIGURE 1 | Neuropsychological profile of executive functions in patients with deficit and non-deficit schizophrenia (abbreviations in note in **Table 3**).

be useful for differentiating between deficit and NDS remains a matter for further discussion. The SCWT has not been used with Relative Inhibition in previous research. Though, in the work of Buchanan et al. (1994), patients with DS obtained lower scores on the interference index, which was modified using statistical control of the reaction time in the congruent variant, than did patients with NDS. In addition, only the work by Réthelyi et al. (2012) found that patients with DS had longer response times in the incongruent variant of this task than patients with NDS, but these results may reflect a greater slowing of information processing, rather than large deficits in cognitive inhibition (Knowles et al., 2010). It was also observed that DS and NDS patients obtained similar results in motor response, based on their performance of the GNG. The groups did not differ in terms of inhibiting reactions to irrelevant stimuli (No Go). The existence of any larger deficits in patients with DS than those with NDS in the area of cognitive and motor inhibition requires further research, especially in the context of the assessment of brain activity using functional neuroimaging techniques (Egner and Hirsch, 2005; Aron et al., 2007; Gorfein and MacLeod, 2007; Yücel et al., 2014).

A partial confirmation of the second hypothesis was possible, as we have shown the presence of a relationship between certain aspects of executive function, both in patients with DS and NDS. There were, however, some discrepancies between the patient groups. In both groups there were associations between concept formation, problem-solving, and non-verbal cognitive flexibility. Only in patients with DS were there links between concept formation and cognitive inhibition. In turn, significant correlations between concept formation, problem-solving, and verbal cognitive flexibility were only present in patients with NDS. However, it was difficult to relate these results to the findings of other authors, as the relationship between various executive domains in patients with DS and NDS has not been studied very deeply. Admittedly, Yu et al. (2015) reported that there is an important correlation between performance on the TMT and VFT P in patients with DS. A similar relationship was observed in this study, since there was an association between the TMT Relative Flexibility Indicator and the VFT P.

The third hypothesis was confirmed, as we have demonstrated the presence of significant variation in terms of levels of the individual aspects of executive function in patients with DS and NDS. It was found that, in both groups, patients were weaker in the area of verbal cognitive flexibility than in other executive domains. In addition, patients of both groups performed at the same level in terms of concept formation, problem-solving, and motor inhibition. In turn, non-verbal cognitive flexibility and cognitive inhibition remained at a higher level than verbal cognitive flexibility, but still proved significantly more difficult than the rest of the executive domains. The fact that the executive function profiles in both groups were similar was shown by the small effect size (0.03) of differences in the comparison of overall scores in ANOVA, which means that the analysis explained only 3% of the variation of the general results of the two groups. Our results were consistent with the results obtained by Brazo et al. (2002) and Cascella et al. (2008). Réthelyi et al. (2012) and Yu et al. (2015) reported slightly different results – finding that DS patients exhibited greater difficulties with non-verbal than with verbal cognitive flexibility. The obtained results were partially in line with the results of Chen et al. (2014). They found modest differences between the neuropsychological profiles of first-episode drug naive patients with DS and NDS, as well as between medicated patients with DS and NDS. However, only in the case of the first-episode drug naive patients were differences found between particular cognitive domains – i.e., patients with DS scored lower than those with NDS in terms of speed of processing and attention. However, it was difficult to directly compare the results presented in this paper to those of Chen et al. (2014) because the latter authors used different measurement tools (i.e., the CogState battery) for evaluating cognitive functions.

CONCLUSION

The results in this paper are in line with other research and require further empirical validation. An important strength of this study was the use of a neuropsychological test battery for assessing various aspects of executive function in a large patient group. With this data it was possible to consider a broader diagnostic context, which could inform the work of therapeutic teams (Mak et al., 2013). In particular, the ability to detect deficit patients early on in the course of their disease and identify specific executive domains which are impaired may facilitate the implementation of rehabilitation activities, which can help patients function in society (Semkovska et al., 2004; Zipursky, 2014). One limitation of this study would be the lack of control group (e.g., healthy subjects). However, the main goal was to examine the differences between the two types of schizophrenia, which the authors believe has been achieved. Due to the complex nature of the relationship between brain and behavior, the results

of neuropsychological assessment can only suggest a complex neural network dysfunction responsible for performing specific executive functions, which may be another potential limitation of this study (Alexander et al., 2012). Future projects might focus on the assessment of executive function and working memory in deficit patients, based on functional magnetic resonance imaging as well as the assessment of the consequences of impaired executive function on psychosocial functioning in deficit and NDS patients.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of Bioethical Commission of the Pomeranian Medical University with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Bioethical Commission of the Pomeranian Medical University.

AUTHOR CONTRIBUTIONS

All authors contributed to and have approved the final manuscript. JP-W was the principal coordinator of the grant, was involved in the study design, and took part in patient recruitment. ET managed literature searches and analyses, performed statistical analysis, wrote the first draft of the manuscript and took part patient recruitment. JS was involved in conceptualization of the project, study design, and corrected the manuscript. MM took part in patient recruitment. AS took part in patient recruitment. PB took part in patient recruitment.

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frontiers in Psychiatry

REVIEW
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A Brief Assessment of Intelligence Decline in Schizophrenia As Represented by the Difference between Current and Premorbid Intellectual Quotient

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Patients with schizophrenia elicit several clinical features, such as psychotic symptoms, cognitive impairment, and subtle decline of intelligence. The latter two features become evident around the onset of the illness, although they may exist even before the disease onset in a substantial proportion of cases. Here, we review the literature concerning intelligence decline (ID) during the progression of schizophrenia. ID can be estimated by comparing premorbid and current intellectual quotient (IQ) by means of the Adult Reading Test and Wechsler Adult Intelligence Scale (WAIS), respectively. For the purpose of brief assessment, we have recently developed the WAIS-Short Form, which consists of Similarities and Symbol Search and well reflects functional outcomes. According to the degree of ID, patients were classified into three distinct subgroups; deteriorated, preserved, and compromised groups. Patients who show deteriorated IQ (deteriorated group) elicit ID from a premorbid level (≥10-point difference between current and premorbid IQ), while patients who show preserved or compromised IQ do not show such decline (<10-point difference). Furthermore, the latter patients were divided into patients with preserved and compromised IQ based on an estimated premorbid IQ score >90 or below 90, respectively. We have recently shown the distribution of ID in a large cohort of schizophrenia patients. Consistent with previous studies, approximately 30% of schizophrenia patients had a decline of less than 10 points, i.e., normal intellectual performance. In contrast, approximately 70% of patients showed deterioration of IQ. These results indicate that there is a subgroup of schizophrenia patients who have mild or minimal intellectual deficits, following the onset of the disorder. Therefore, a careful assessment of ID is important in identifying appropriate interventions, including medications, cognitive remediation, and social/community services.

Keywords: schizophrenia, intelligence decline, premorbid intellectual quotient, current intellectual quotient, Wechsler Adult Intelligence Scale

INTELLIGENCE DECLINE (ID) IN SCHIZOPHRENIA

Schizophrenia is a common and complex psychiatric disorder with clinical and genetic heterogeneity (1). The lifetime risk of the disorder is approximately 0.5–1% (2). The disorder is characterized by a wide spectrum of symptoms, such as delusions, hallucinations, blunted affect and withdrawal, cognitive impairments, as well as subtle decline in intelligence. Cognitive impairments in numerous and diverse domains, including attention, working, verbal and visual memories, processing speed, social cognition, and general intelligence (i.e., a 1- to 2-SD decline in performance on neuropsychological tests compared with healthy individuals), are a core feature of the disorder and a reasonable target for treatment (3–9). These deficits contribute to social or occupational dysfunction and poor life outcomes (10–12). Cognitive impairments and psychotic symptoms are relatively independent dimensions of the disorder (13). Cognitive impairments are exhibited around or after the onset of schizophrenia, while, in a substantial proportion of cases, the impairments exist even before the disease onset (14–16). On the other hand, intelligence decline (ID) represents intra-individual differences in intellectual quotinent (IQ) at different time points, such as before and after the onset of morbidity (13, 17, 18). In this article, we review the literature concerning ID during the progression of schizophrenia.

A BRIEF ASSESSMENT OF ID IN SCHIZOPHRENIA

Intelligence decline is defined as a decrease in current intellectual quotient (IQ) from a premorbid level in patients with schizophrenia (13, 17, 18). ID can be estimated by comparing standard assessments of estimated premorbid and current IQ using the Adult Reading Test and the Wechsler Adult Intelligence Scale (WAIS), respectively. The WAIS has been widely used to measure current intellectual performance in patients with psychiatric disorders as well as healthy subjects. The battery has been updated several times [WAIS (19); WAIS-R (20); WAIS-III (21); and WAIS-IV (22)]. To represent the intellectual construct in a healthy subjects, the four factors, Verbal Comprehension (VC), Working Memory (WM), Perceptual Organization (PO), and Processing Speed (PS), were established in the WAIS-III (**Figure 1**). VC and WM are components of verbal IQ (VIQ), while PO and PS are components of performance IQ (PIQ). In the updated WAIS-IV, the dual IQ (VIQ and PIQ) scoring system was eliminated, and the concept of index-based assessment of intelligence has been further enhanced. Furthermore, two subtests (Object Assembly and Picture Arrangement and) in the WAIS-III were replaced by newer subtests (Figure Weights and Visual Puzzles) in the WAIS-IV to enhance psychometric validity and user friendliness (23).

It takes 60–95 min to administrate the WAIS in healthy subjects. As it has been concerned about the lengthy administration time for the WAIS, it has been made efforts to develop the WAIS-Short Form (WAIS-SF) (23–26). The typical approach to developing the WAIS-SF was to select subtests to optimize the prediction of full-scale IQ (FIQ) and/or retain the representativeness of the IQ structure (26). However, it is presumed that the four-factor structure for healthy subjects does not need to be preserved in patients with schizophrenia (23, 26); e.g., if VC and WM were collapsed into a single factor in patients with schizophrenia, selecting a subtest from each of these domains would be redundant (26). Another problem for previous WAIS-SFs is the lack of association with real-world outcomes. The WAIS-SF for schizophrenia would be more useful if it reflected functional outcomes, such as activities of daily living or social functioning.

We have recently developed an optimal WAIS-III SF to assess current intellectual performance in patients with schizophrenia (23) according to the following five criteria: (i) prediction of FIQ,

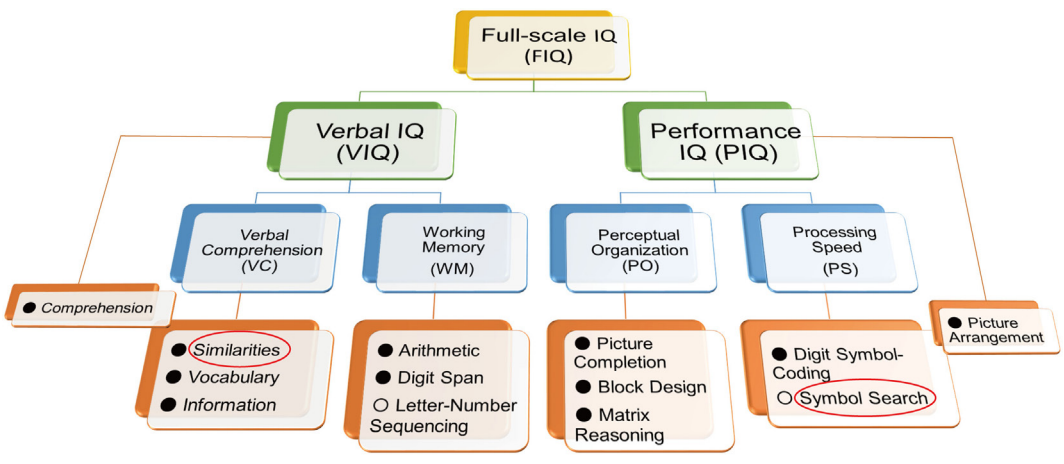

FIGURE 1 | Structure of the Wechsler Adult Intelligence Scale (WAIS)-III. To shorten administration time and assess functional outcome in patients with schizophrenia, we previously developed the WAIS-III Short Form using the Similarities and Symbol Search components (red circles) (23). The administration time was shortened to approximately 10 min. Letter-Number Sequencing and Symbol Search (○) are not used for calculation of verbal intellectual quotient (VIQ) and performance intellectual quotient (PIQ), respectively.

(ii) representativeness of the IQ structure, (iii) consistency of subtests across versions (WAIS-III and IV), (iv) relation to functional outcomes (daily living skills and social functioning) assessed by the UCSD Performance-based Skills Assessment [UPSA; (27)] and the Social Functioning Scale [SFS; (28, 29)], and (v) conciseness in terms of administration time. To select subtests meeting (i) and (ii) criteria, we first conducted an exploratory factor and multiple regression analyses in patients with schizophrenia, and candidate subtests were nominated to produce a candidate SF. The coverage of VIQ and PIQ and the consistency of subtests across WAIS versions, according to (iii) criterion, were also considered in the nomination process. In terms of ability to explain the variance of FIQ, correlations with functional outcomes, and time saved in comparison to full administration of the WAIS, the candidate SFs were finally examined. We found that the dyad of Similarities from verbal intellectual ability and Symbol Search from performance intellectual ability showed the highest correlations with functional outcomes and allowed the shortest administration time (**Figure 1**). It takes approximately 10 min to administer the WAIS-SF (Similarities and Symbol Search). It is considered that variation in processing speed is the basis of individual differences in intellectual function (13). In addition, slow cognitive processing in patients with schizophrenia is essential to the clinical manifestation of the disorder (30). Symbol Search is a constituent of the PS factor of the WAIS (**Figure 1**); therefore, this item is useful on the WAIS-SF for schizophrenia.

DISTRIBUTION OF ID IN SCHIZOPHRENIA

The National Adult Reading Test (NART), the Wechsler Test of Adult Reading (WTAR), and the Wide Range Achievement Test (WRAT) scores are correlated with cognitive ability in healthy subjects, and scores on the NART, the WTAR, and the WRAT had high stability overtime (31–33). The accuracy of IQ estimates using the NART is higher than that using the WTAR (31, 32), and the WTAR is a slightly more reliable test of IQ estimates than the WRAT in a more educated and higher-functioning population (33). The NART, the WTAR, and the WRAT are three tests developed to estimate premorbid IQ because reading ability is measured as relatively intact in patients with schizophrenia (34), and its validity has been confirmed in English-speaking schizophrenia patients (13, 35, 36). The Japanese version of the NART [JART; (37)] is also widely used for Japanese-speaking patients to estimate premorbid IQ, as an equivalent to the NART (6, 7, 38–42). The stability of premorbid IQ assessed by the NART in patients with schizophrenia has been prospectively demonstrated in a longitudinal study (43). On the other hand, estimation of premorbid IQ retrospectively by these tests has a limitation. A longitudinal study design allowing long-term follow-up of high risk groups with baseline and follow-up IQ assessments is the only way to eliminate this limitation.

According to the categorization method described in previous studies (13, 44–51), patients with schizophrenia are typically classified by degree of ID into three distinct intellectual level subgroups: deteriorated, preserved, and compromised IQ.

(i) Deteriorated IQ: patients who show an ID as measured by a difference of 10 points or more between estimated premorbid and current IQ.
(ii) Preserved IQ: patients with less than a 10-point difference between estimated premorbid and current IQ and with an estimated premorbid IQ score >90.
(iii) Compromised IQ: patients with less than a 10-point difference between estimated premorbid and current IQ and with an estimated premorbid IQ below 90.

The frequencies of preserved, deteriorated, and compromised IQ in patients with schizophrenia are summarized in **Table 1** (13, 18, 44–51). For example, Weickert et al. (44) reported that 25% were categorized as having preserved IQ, 51% displayed deteriorated IQ, and 24% showed compromised IQ among 117 patients with schizophrenia. Badcock et al. (13) reported that 41% displayed preserved IQ, 43% were categorized as having deteriorated IQ, and 16% displayed compromised IQ among the 109 patients with schizophrenia. However, the distribution of ID in patients with schizophrenia was not examined in depth. Thus, we recently reported on the distribution of the ID in a large cohort of 446 patients with schizophrenia (18). Consistent with

TABLE 1 | Frequencies of preserved, deteriorated, and compromised IQ in patients with schizophrenia.

Study name	*n*	Preserved IQ	Deteriorated IQ	Compromised IQ	Diagnostic criteria	Participants	Assessment of premorbid IQ
Weickert et al. (44)	177	24.8% (29)	51.3% (60)	23.9% (28)	DSM-III-R	SCZ	WRAT
Badcock et al. (13)	109	41.3% (45)	43.1% (47)	15.6% (17)	DSM-IV or ICD-10	SCZ	NART
Kremen et al. (46)	80	27.5% (22)	50.0% (40)	22.5% (18)	DSM-III-R	SCZ	WRAT
Potter and Nestor (49)	73	28.8% (21)	28.8% (21)	42.5% (31)	DSM-IV	SCZ or SD	WRAT
Leeson et al. (47)	129	31.0% (40)	44.2% (57)	24.8% (32)	DSM-III-R or ICD-10	first-episode SCZ or SD	WTAR
Mercado et al. (48)	149	26.8% (40)	39.6% (59)	33.6% (50)	DSM-IV	SCZ or SD	Information subtest of the WAIS-III
Ammari et al. (45)	72	44.4% (32)	36.1% (26)	19.4% (14)	DSM-IV	SCZ or SD	WRAT
Wells et al. (51)	534	29.4% (157)	44.8% (239)	25.8% (138)	DSM-IV	SCZ or SD	WTAR
Weinberg et al. (50)	96	26.0% (25)	62.5% (60)	11.5% (11)	DSM-IV	SCZ or SD	WTAR
Fujino et al. (18)	446	27.1% (121)	69.3% (309)	3.6% (16)	DSM-IV or ICD-10	SCZ	JART

SCZ, schizophrenia; SD, schizoaffective disorder; WRAT, Wide Range Achievement Test; NART, National Adult Reading Test; WTAR, Wechsler Test of Adult Reading; WAIS, Wechsler Adult Intelligence Scale; JART, Japanese version of the NART; IQ, intellectual quotient.

previous studies (13, 44–51), approximately 30% of patients with schizophrenia had a decline of less than 10 points, i.e., normal performance. In contrast, approximately 70% of patients showed deteriorated IQ: a severe decline of 30 points or greater (13.5%), a moderate decline of 20–30 points (26.3%), a mild decline of 15–20 points (15.9%), or a borderline decline of 10–15 points (13.7%) (**Figure 2**). The estimated premorbid IQ in our study (mean ± SE = 100.5 ± 0.5) was higher than those in previous studies [Weickert et al. (44), 97.1 ± 1.0: Badcock et al. (13), 95.0 ± 0.7: Leeson et al. (47), 91.0 ± 0.7]. This difference might be derived from the inclusion criteria, by which our study basically excluded schizophrenia patients who had lower estimated premorbid IQ, such as mental retardation (18), i.e., some patients with compromised IQ were initially excluded from the cohort.

A "NEUROPSYCHOLOGICALLY NORMAL" SCHIZOPHRENIA GROUP

Social/occupational dysfunction that is remarkably below the level achieved prior to the onset is listed as a diagnostic hallmark for schizophrenia in the DSM-IV and 5 criteria (52); however, neuropsychological impairments were not included in the criteria. As mentioned in the above section, no more than approximately 30% of schizophrenia patients are entirely free of neuropsychological impairments, although there is heterogeneity in this proportion among studies (13, 18, 44, 46, 47, 53, 54). If cognitive impairments are a core feature of schizophrenia, it may be difficult to explain the presence of neuropsychologically normal function in schizophrenia patients who display the full clinical syndrome.

A cluster-analysis approach can group patients on the basis of profiles or patterns of cognitive impairments and produce more homogeneous groupings (1, 55), providing an opportunity to classify patients. Cluster-analysis studies of cognitive function within schizophrenia patients have successfully created meaningful subgroups with at least three clusters: patients who are neuropsychologically normal, patients with intermediate cognitive deficits, and patients with widespread deficits (1, 54–60). One consideration is that schizophrenia patients who have mild ID or are neuropsychologically normal may be a unique subtype and may comprise a relatively benign subtype of schizophrenia in terms of prognosis. This type of patient may be better educated and/or have higher premorbid IQ than patients with impaired cognitive function. Indeed, some studies have indicated that patients with preserved IQ tended to be better educated and/or show higher premorbid IQ than patients with deteriorated or compromised IQ (13, 44, 47), while other studies have not indicated such associations (46).

On the other hand, schizophrenia patients with preserved IQ exhibited specific deficits in at least some cognitive domains, especially executive function and attention, compared with healthy subjects who had similar IQ, even though that subset of patients had apparently normal current intellectual function (13, 44, 53, 61, 62). These studies suggest that ID, although typical of schizophrenia, is not universally characteristic and that executive function and attention deficits may be core features of schizophrenia, independent of intelligence variations (44). However, not only IQ decline but also executive function and attention deficits may be less than universally characteristic of patients with schizophrenia because the disorder is clinically heterogeneous. We suggest that it is necessary to make a detailed, personalized assessment of cognitive impairments, such as IQ decline and executive function and attention deficits, in order to treat functional impairments appropriately in schizophrenia patients. As shown in **Figure 3**, we additionally suggest an algorithm to be employed in the treatment of intellectual impairments in schizophrenia patients. First, we measure intellectual function in patients with schizophrenia using estimated premorbid and current IQ, and we assess whether the patient has intellectual impairment. According to the status of intellectual impairment, we assess employment-related problems in each patient and treat those problems. The ultimate goal is for the patient to work at a premorbid level.

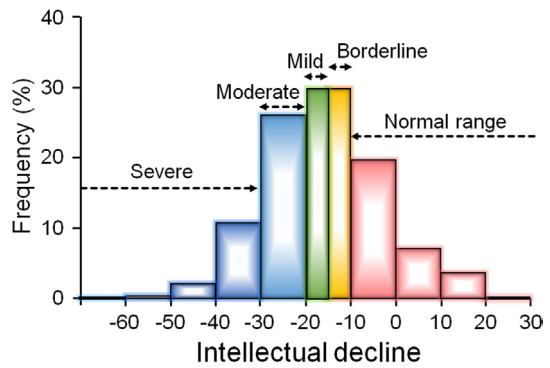

FIGURE 2 | The distribution of intelligence decline (ID) in a large cohort of 446 patients with schizophrenia (18). The article by Fujino et al. (18) is published under the Attribution-Noncommercial-No Derivatives (CC BY-NC-ND) Creative Commons license, and permissions of the modification have been obtained from publisher. Approximately 30% of patients had no evidence of ID (a decline less than 10 points), while approximately 70% of patients showed deteriorated intellectual quotient: a borderline decline of 10–15 points (14%), a mild decline of 15–20 points (16%), a moderate decline of 20–30 points (26%), or a severe decline of 30 points or greater (14%).

PATHOPHYSIOLOGY OF COGNITIVE IMPAIRMENTS IN SCHIZOPHRENIA

Schizophrenia has a strong genetic basis with an estimated heritability of approximately 80% (63). Most cognitive functions also have a genetic component and are heritable (h^2 = 0.33–0.85) (64–68). Impairments such as cognitive decline are stable, partly affected by antipsychotic medications (47, 69–71), and typically stronger in schizophrenia patients (72). Cognitive dysfunctions have also been shown in the unaffected relatives or twin siblings of people with schizophrenia (73). Previous genome-wide association studies (GWASs) on schizophrenia and cognitive functions have indicated that many genes or genetic variants mediate both cognitive function and the risk of schizophrenia (7, 17, 73–77). These previous GWASs on schizophrenia and cognitive function have explained up to approximately 20%

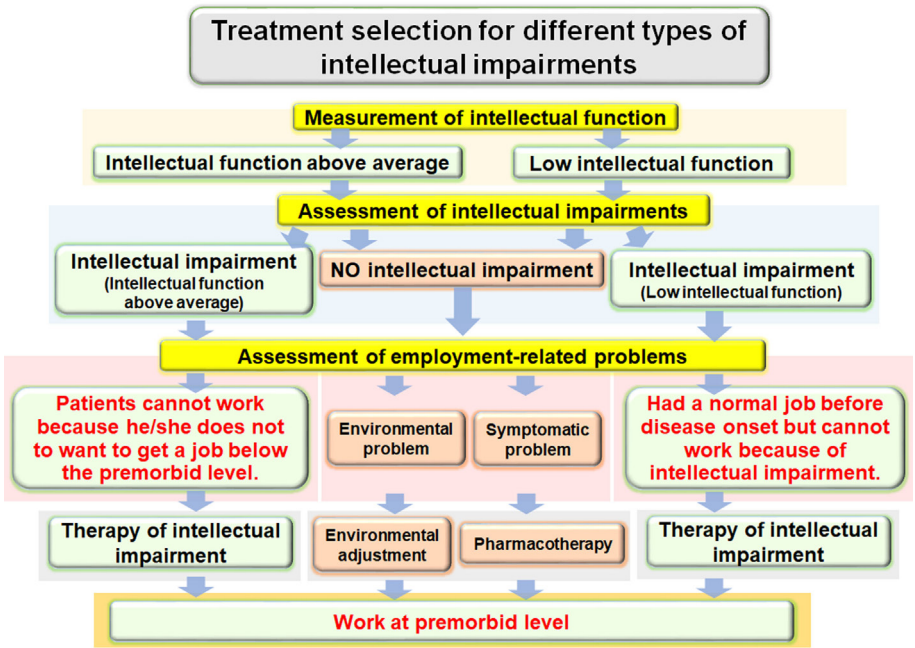

FIGURE 3 | Algorithm for treatment of intellectual impairments in patients with schizophrenia to improve employment outcomes.

of the genetic architecture of risk for schizophrenia and poor cognitive function (74–77). In addition, a part of the phenotypic correlation between cognitive function and schizophrenia results from identical genetic effects (73, 77). Polygenic risk scores for cognitive dysfunction were associated with a higher risk of schizophrenia, whereas polygenic risk scores for schizophrenia were associated with lower cognitive ability (73, 77, 78). Thus, cognitive functions have been proposed as a useful intermediate phenotype (39, 79–82) to understand the genetic mechanisms involved in the pathophysiology of schizophrenia.

We suggest that genetic variants related to cognitive impairments including ID might be associated with the *N*-methyl-D-aspartate (NMDA) glutamate network (7) or in delta(4)-desaturase, sphingolipid 2 (*DEGS2*) gene expression (17, 83). Glutamate is the major excitatory neurotransmitter of the central nervous system (CNS) and is involved in basic neuronal functions and CNS processes, including memory, learning, and synaptic plasticity (84). Decreased function of glutamate transmission through NMDA receptors that are voltage-dependent ionotropic glutamate receptors has been involved in the pathophysiology of schizophrenia (85). NMDA receptor antagonists, including phencyclidine and ketamine, can induce schizophrenia-like psychotic symptoms and cognitive impairments in individuals without schizophrenia and exacerbate symptoms in schizophrenia patients (86, 87). Schizophrenia patients have aberrant density and subunit composition of NMDA receptors in the postmortem brains (88, 89).

From birth onward, the *DEGS2* gene is most abundantly expressed in the dorsolateral prefrontal cortex (DLPFC) that is a major component of the high-order associative cortex related to both schizophrenia and cognitive functions (83, 90). Carriers of the ID-associated risk allele had lower *DEGS2* expression than subjects homozygous for the non-risk allele in the DLPFC (17, 83). The *DEGS2* enzyme is implicated in the biosynthesis of phytosphingolipids. Sphingomyelin is a type of sphingolipid, and abnormalities of the sphingomyelin can cause several CNS diseases, including schizophrenia (91, 92). The low expression pattern of *DEGS2* is correlated with the low distribution of phytosphingolipids (93, 94). The *DEGS2* risk polymorphism related to low *DEGS2* expression in the DLPFC may be associated with lower synthesis of sphingolipids in the brain because *DEGS2* mRNA expression regulates synthesis of phytosphingolipids during keratinocyte differentiation (93). Further research is needed to clarify the role of glutamate network and *DEGS2* gene expression in the pathogenesis of ID of schizophrenia.

EFFECTS OF ANTIPSYCHOTICS ON ID IN SCHIZOPHRENIA

Positive symptoms and negative symptoms have become targets for medication in patients with schizophrenia. However, based on the evidence that the functional disability accompanying schizophrenia is strongly associated with cognitive impairments and is not correlated with psychotic symptoms (12), we should focus on ID in patients with schizophrenia. The therapeutic effects of antipsychotics are predominantly limited to the positive and negative symptoms, and those drugs have substantially less impact on improvement of cognitive impairments. It has been reported that typical antipsychotics are applied without regard for cognitive impairments in patients with schizophrenia and do little to

improve them (84, 95), whereas atypical antipsychotics have been reported to partly reduce cognitive impairment in schizophrenia patients (84, 95, 96). Atypical antipsychotics are superior to typical antipsychotics at improving cognitive impairment (effect size = 0.24), although there are no differences in improvement among atypical antipsychotics (97). Such improvements are also observed in specific studies of first-episode schizophrenia and early-onset schizophrenia (98–100).

To date, the mechanisms whereby antipsychotics act on ID have remained unclear. Atypical antipsychotics produce extensive blockade of serotonin $(5\text{-HT})_{2A}$ receptors, direct or indirect stimulation of 5-HT_{1A} receptors, and, to a lesser extent, a reduction in dopamine D2 receptor-mediated neurotransmission (101–103). The serotonergic actions of the atypical antipsychotics are able to mitigate cognitive impairments in patients with schizophrenia (103). In addition, 5-HT_6 or 5-HT_7 receptor antagonists may also contribute to the beneficial effects of the antipsychotics on cognitive function (103).

Furthermore, anticholinergic load is related to lower cognitive function in schizophrenia patients (104, 105). The administration rate of anticholinergic medications is lower in patients who are prescribed atypical antipsychotics compared with those who are prescribed typical antipsychotics, supporting the idea that cognitive improvements would differ between users of typical and atypical antipsychotics. The discontinuation of long-term anticholinergic use would mitigate cognitive impairment in patients with schizophrenia (105, 106). In addition, the use of benzodiazepines is related to cognitive impairments in schizophrenia patients (107, 108). The reduction or discontinuation of long-term benzodiazepines with atypical antipsychotics ameliorates cognitive impairments in patients with schizophrenia (108). These findings suggest that the use of anticholinergics and long-term benzodiazepines would be related to cognitive impairments in patients with schizophrenia. Therefore, we suggest that physicians should prescribe only atypical antipsychotics, without anticholinergics or benzodiazepines, to reduce the cognitive impairments observed in schizophrenia. On the other hand, the use of benzodiazepines and anticholinergics would treat unwanted symptoms, such as anxiety and extrapyramidal symptoms, in schizophrenia. The development of novel antipsychotics that are unlikely to result in extrapyramidal symptom or treat anxiety symptom is warranted.

The cognitive impairments observed in schizophrenia may be affected by decreased activity of the M1 muscarinic acetylcholine receptor, dysfunction of NMDA glutamatergic neurotransmission, and serotonergic dysregulation. However, the effects of cholinesterase inhibitors, antidepressants, or 5-HT2 antagonists as adjunctive treatments to antipsychotics for cognitive impairments in schizophrenia have been limited (109–113). Approval of antipsychotic drugs with novel mechanisms of action has been rare in recent years despite extensive efforts by investigators. Further investigations are essential to address this issue by identifying new pharmacological targets related to ID in patients with schizophrenia. We suggest that patients without ID should be initially detected and excluded from putative clinical trials of drugs meant to mitigate ID in patients with schizophrenia.

COGNITIVE REMEDIATION

Cognitive remediation or cognitive rehabilitation interventions are designed to improve cognitive impairments through repeated practice of cognitive tasks and/or strategy training. As the effects of antipsychotics on cognitive impairments in schizophrenia patients have been limited, a number of cognitive remediation programs have been increasingly examined to improve cognitive impairments (114). Randomized controlled studies have shown cognitive remediation to have positive effects on cognitive impairments in patients with first-episode psychosis as well as schizophrenia (114–118). The average effect size was small to moderate at approximately 0.40 (114, 115). Some types of cognitive remediation involve extensive use of computers, while others focus primarily on paper-and-pencil tasks. The Neuropsychological Educational Approach to Remediation (NEAR) is an evidence-based cognitive remediation approach (114). The NEAR program involves a combination of "drill and practice" exercises and teaching strategies to ameliorate cognitive impairments (114). NEAR utilizes commercially available educational software to create a rich learning environment that is intrinsically motivating and rewarding (114). Cognitive remediation interventions are conducted individually or in groups. Although the goal of cognitive remediation is to ameliorate cognitive impairments in patients with schizophrenia, more than 12.0% of participants dropped out at different points during the program (114, 115). Therefore, it may be difficult to generalize a cognitive remediation as a treatment for cognitive impairments in patients with schizophrenia. In addition, it remains unclear whether the improvements are sustained or temporary, although short-term effects of cognitive remediation on cognitive function have been indicated (115). Similar to our proposal regarding the composition of drug trials, we suggest that patients without ID should be initially detected and excluded from clinical trials to develop cognitive remediation programs for patients with schizophrenia.

CONCLUSION

In this study, we reviewed the literature of ID in patients with schizophrenia. Although intellectual impairments are a core feature of schizophrenia, the effects of antipsychotics and cognitive remediation against those impairments have been limited. We have held several workshops on the brief assessment of ID in schizophrenia to promote the concept of monitoring ID in Japanese patients with schizophrenia. Further studies are warranted to develop novel antipsychotics and cognitive remediation for patients with ID.

AUTHOR CONTRIBUTIONS

RH supervised the entire project and was critically involved in the design, analysis, and interpretation of the data. KO, CS, and TS collected the data, wrote the manuscript, and were responsible for performing the literature review. HF, YY, HY, and MF were heavily involved in the collection of the majority of the data and contributed intellectually to the interpretation of the data. All authors contributed to and have approved the final manuscript.

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Verbal Memory Impairment in Patients with Subsyndromal Bipolar Disorder

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Backgrounds: Several domains of cognitive function, including learning memory and executive function, are impaired in mood disorders. Also, the relationship between disturbances of these two cognitive domains has been suggested. In line with the recent initiative to establish a standard measure of cognitive decline in bipolar disorder, the present study was conducted to (1) test the criterion-related validity and test–retest reliability of the California Verbal Learning Test (CVLT)-II Japanese version, and (2) determine if type of word learning tasks (i.e., with or without a category structure) affects severity of verbal memory deficits in patients with subsyndromal bipolar disorder.

Methods: Thirty-six patients with bipolar disorder with mild symptoms and 42 healthy volunteers participated in the study. We first compared effect sizes for memory deficits in patients among the CVLT-II, Brief Assessment of Cognition in Schizophrenia (BACS), and Hopkins Verbal Memory Tests-Revised (HVLT-R). We next evaluated the correlations between scores of the CVLT-II vs. those of the BACS and HVLT-R. Bipolar patients were re-assessed with the same (standard) or alternate forms of the CVLT-II and HVLT-R 1 month later.

Results: Scores on the CVLT-II 1–5 Free Recall and Long-delay Free Recall, as well as the HVLT-R Immediate Recall, but not the BACS List Learning were significantly lower for patients compared to control subjects. The effect sizes for cognitive decline due to the illness were comparable when measured by the CVLT-II and HVLT-R, ranging from 0.5 to 0.6. CVLT-II scores were significantly correlated with those of the HVLT-R and BACS. Test–retest reliability of the CVLT-II was acceptable, and no significant practice effect was observed when the alternate form was used. There was no consistent relationship between mood symptoms and performance on the CVLT-II.

Conclusion: These results suggest the CVLT-II Japanese version is able to discriminate between bipolar disorder patients and healthy controls with good sensitivity and validity. Data in this study also indicate that the degree of verbal memory deficits in bipolar disorder may be influenced by memory organizational strategy.

Keywords: bipolar disorder, verbal learning, California Verbal Learning Test-II, HVLT-R, Brief Assessment of Cognition in Schizophrenia

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INTRODUCTION

Bipolar disorder is associated with poor psychosocial outcome not only in the manic or depressive state, but also in the subsyndromal state (1–3). Patients with the illness demonstrate impairments in several cognitive domains even during the euthymic phase (4). The profile of cognitive disturbances of bipolar disorder has been reported to be similar to that of schizophrenia (5–7), with less severity. Thus, the effect size of euthymic patients ranges from 0.4 to 0.7 compared to healthy controls (8). Specifically, Martínez-Arán et al. (9) demonstrated that duration of illness, a history of psychotic symptoms, number of hospitalizations, manic episodes, and suicide attempts were positively related to cognitive impairments. Importantly, cognitive impairments have been suggested to predict poor psychosocial outcome in bipolar disorder patients (10–12).

There may be interactions in the disturbances of key cognitive domains in bipolar disorder. For example, the contribution of executive function to learning memory has been reported in patients with the disease (13). Specifically, Deckersbach et al. (13) report that verbal learning memory deficits are mediated by semantic clustering encoding (memory organization) strategies. This finding may be important in understanding the nature of cognitive impairment of mood disorders.

To evaluate verbal memory in subjects with bipolar disorder, several tasks, including the Brief Assessment of Cognition in Schizophrenia (BACS) (14), Hopkins Verbal Learning Test-Revised (HVLT-R) (15), and the California Verbal Learning Test (CVLT) (16, 17) have been used. For example, the CVLT has been recommended to assess verbal learning in bipolar disorder (16). In this line, the reliability of the CVLT-II has been reported to be acceptable with good internal consistency, whose normative data have been shown to be more representative of the general population than that for the CVLT (18).

The effect size of cognitive decline in euthymic patients ranges from 0.66 to 0.90 (19). As verbal (learning) memory provides one of the important domains of cognition in psychiatric diseases (20), it is worthwhile to explore which factors contribute to its impairment in bipolar patients whose mood symptoms are not so eminent. Since executive function, another pivotal domain of cognition related to frontal lobe function, is impaired in euthymic bipolar patients (21), it is hypothesized that verbal memory deficits become evident when assessed with word list tasks that require memory organizational strategy, but not those that do not require it.

The main purpose of this study was to investigate the impact of memory organizational strategies on verbal (learning) memory, as measured by performance on word list tasks, in patients with bipolar disorder. For this aim, we sought to determine whether the CVLT-II and HVLT-R, but not the BACS would be able to discriminate between patients with subsyndromal bipolar disorder and normal control subjects. This is based on the assumption that only the former two tasks require subjects to use memory organization. Additionally, we investigated the validity and reliability of the Japanese version of CVLT-II using the BACS List Learning and HVLT-R as reference measures of verbal learning and memory. Preliminary analyses of the present data have been reported (22, 23).

MATERIALS AND METHODS

Subjects

This was a multi-center collaborative study, whose design, characteristics of participants, and other information have been registered (UMIN ID: 000013623). The sample consisted of 78 participants; 36 individuals with bipolar disorder and 42 healthy control participants who were native Japanese and had no history of psychiatric disorders (**Table 1**). Bipolar disorder patients were diagnosed by clinicians according to DSM-IV criteria and showed a subsyndromal or non-significant clinical level of severity of mood symptoms, i.e., ratings with the Montgomery–Asberg Depression Rating Scale (MADRS) ≤14 and the Young Mania Rating Scale (YMRS) ≤14 (24). The patients were recruited from the National Center of Neurology and Psychiatry Hospital, Fujita Health University Hospital, Nagoya University Hospital and Hokkaido University Hospital. Healthy volunteers as a control group were recruited from the local community. They were matched with bipolar disorder patients in terms of age and sex (**Table 1**). There were no between-group differences in educated years and premorbid IQ estimated using the Japanese Adult Reading Test (25). Patients with comorbid neurological illness, previous traumatic brain injury with any known cognitive consequences or loss of consciousness for more than 5 min, or alcohol/substance abuse or addiction (except nicotine) were excluded. Six patients had a history of suicide attempt and two received electroconvulsive therapy. The patients were taking lamotrigine (for 16 cases), lithium (15), aripiprazole (14), valproate (11), quetiapine (9), olanzapine (3), carbamazepine (2), risperidone (2), sertraline (2) and levomepromazine (2), chlorpromazine (1), duloxetine (1), and maprotiline (1).

Written consent was obtained from all participants, according to ethics guidelines set out by each participating site. The study protocol was approved by the ethics committees of participating institutions.

The Study Design

The subjects were administered three verbal learning tests twice with an interval of approximately 1 month. Mood symptoms

TABLE 1 | Clinical and demographic variables (mean ± SD).

	Bipolar disorder	Healthy controls
Sex (male:female)	12:24	17:25
Age (years)	39.2 ± 9.2	36.9 ± 10.0
Type (A-A:A-B)	17:19	18:24
Educated years	15.0 ± 2.4	14.1 ± 2.1
JART	107.0 ± 9.2	106.9 ± 8.2
MADRS	6.2 ± 4.4	–
YMRS	2.3 ± 3.1	–
Subtype (BP1:BP2)	9:27	–
Non-remission patients	9	–
History of psychosis	8	–
Duration of illness (months)	92.0 ± 1.1	–
Number of hospitalization	1.1 ± 1.6	–

A-A, standard–standard; A-B, standard–alternate; JART, Japanese Adult Reading Test; MADRS, Montgomery–Asberg Depression Rating Scale; YMRS, Young Mania Rating Scale.

were also assessed each time using the MADRS and YMRS. The CVLT-II, BACS, and HVLT-R forms were switched to alternate forms in 43 subjects (from Nagoya University Hospital and Hokkaido University Hospital) at the follow-up (19 patients and 24 controls), whereas 35 subjects (from National Center of Neurology and Psychiatry Hospital and Fujita Health University Hospital) were administered the same standard form at the follow-up (17 patients and 18 controls) as at the baseline. The same raters performed these cognitive tests at baseline and the 1-month follow-up assessments.

Development of the CVLT-II Japanese Version

To develop a Japanese version of the CVLT-II (26), one of the authors (Tomiki Sumiyoshi) translated the original CVLT-II from English to Japanese. Afterward, a person isolated from the translator performed a back-translation. Modifications of some terms were made to fit the local culture. The back-translation of the English version was approved by Pearson Education, Inc., the copyright owner.

Measures of Verbal Learning

California Verbal Learning Test-II

The CVLT-II measures both recall and recognition abilities using two word lists. In the first five trials, immediately after presentation of List A, the subject is asked to recall the words of the list. List A contains 4 words from each of 4 semantic categories, for a total of 16 words. This procedure enables evaluation of semantic clustering ability, the most effective strategy for learning non-systemized verbal information. Subsequently, an interference list (List B) containing 16 words is presented, followed by a recall test. The interference test is followed by a short-delay free recall test and a short-delay cued recall test using List A. Then, following 20-min interval, a long-delay free recall test, long-delay cued recall test, and yes/no recognition test are administered using List A. After the yes/no recognition test, a new approximately 10-min forced-choice recognition test is arbitrarily administered. In the present study, data obtained in the immediate recall test after the first five trials of List A ("1–5 free recall") and a long-delay free recall test were adopted for analyses, which were the candidate measures to be incorporated in the International Society for Bipolar Disorders-Battery for Assessment of Neurocognition (4). We basically intended to use standardized measure for all cognitive tests; however, since it is not available only for the CVLT-II (Japanese version), we used raw scores for this test.

HVLT-R

The HVLT-R consists of a word list, containing 3 words from one of 4 semantic categories, for a total of 12 words. In the first three trials, immediately after presentation of the word list, the subject is asked to recall the words of the list. Subsequently, following a 20–25-min interval, a delayed recall test is administered. Immediately after the delayed recall test, a forced-choice recognition test is administered. In the present study, the delayed recall test and forced-choice recognition test were not included for brevity, and only a standardized measure in the immediate recall test after the first three trials was adopted for analyses, which is used in the MATRICS Consensus Cognitive Battery (the standardized measure was obtained by using the mean level of 28.2 and the SD of 4.3).

Brief Assessment of Cognition in Schizophrenia

The BACS List Learning test consists of a word list, containing 15 words. The subject is asked to recall the words of the list immediately after presentation of the word list, which was repeated five times. The words in the list were not semantically organized unlike the case in the CVLT-II and HVLT-R. In the present study, a standardized measure in the immediate recall test after the first five trials was adopted for analyses. (The standardized measure was obtained by using the mean level of 49.2 and the standard deviation of 9.9.) (27).

Statistical Analysis

Student's *t*-test was performed to explore between-group differences for CVLT-II 1–5 free recall scores and long-delay free recall scores, HVLT-R immediate recall scores, and BACS list learning scores at baseline. If a significant between-group difference in either measure was found, the effect size was calculated using a Cohen's *d* to explore its sensitivity. To examine the effect of mood symptoms, Spearman's rank correlation was performed between CVLT-II 1–5 free recall or long-delay free recall scores vs. MADRS and YMRS scores. Test–retest reliability was evaluated using intraclass correlation coefficient (ICC) (28) between scores at baseline and 1-month follow-up for each measure. In addition, practice effect was evaluated using repeated measures ANOVA using "time" as an intra-individual factor and "Group" and "type (A-A, A-B)" as inter-individual factors. Secondary analyses were performed when a significant interaction between the factors was obtained.

To examine the criterion-related validity of the CVLT-II measures, Pearson's product-moment correlation among scores of the CVLT-II 1–5 Free Recall and Long-Delay Free Recall, HVLT-R Immediate Recall, and BACS List Learning was calculated for patients.

RESULTS

Between-Group Comparison of Verbal Learning Measures

Student's *t*-test revealed a significant between-group difference for the CVLT-II 1–5 Free Recall ($t = -2.28$, $P = 0.025$) and Long-Delay Free Recall ($t = -2.04$, $P = 0.035$), and HVLT-R Immediate Recall ($t = -2.47$, $P = 0.016$), but not the BACS List Learning ($t = -1.58$, n.s.) (**Figure 1**). The effect sizes of performance on the measures that showed between-group differences were 0.52, 0.46, and 0.56, respectively. Significant positive correlations were noted between ratings with the MADRS vs. scores of the CVLT-II 1–5 Free Recall (Rho = 0.36, $P = 0.029$), and Long-Delay Free Recall (Rho = 0.34, $P = 0.044$). On the other hand, performances on these CVLT measures were not correlated with YMRS scores (1–5 Free Recall, Rho = 0.12, n.s.; Long-Delay Free Recall, Rho = 0.03, n.s.).

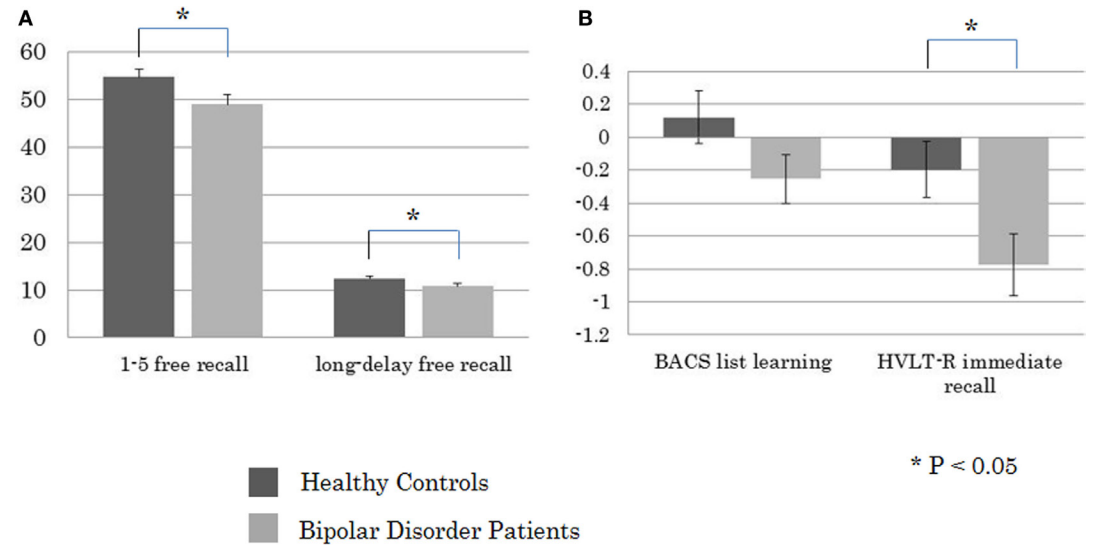

FIGURE 1 | Between-group comparisons in performance on **(A)** the California Verbal Learning Test-II 1–5 free recall and long-delay free recall (presented in raw score), and **(B)** the Brief Assessment of Cognition in Schizophrenia (BACS) list learning and HVLT-R immediate recall (presented in *z*-score).

Test–Retest Reliability and Practice Effect of Verbal Learning Measures

The ICCs between the baseline and 1-month follow-up scores for the BACS List Learning, HVLT-R Immediate Recall, CVLT-II 1–5 Free Recall and Long-Delay Free Recall are summarized in **Table 2**. Good to excellent test–retest reliability was noted in most of the measures.

TABLE 2 | Intraclass correlation coefficients between the baseline and 1-month follow-up scores.

		Bipolar disorder	Healthy controls
Brief Assessment of Cognition in Schizophrenia list learning		0.65	0.57
	A-A	0.84	0.52
	A-B	0.37	0.62
HVLT-R immediate recall		0.83	0.78
	A-A	0.88	0.82
	A-B	0.74	0.73
California Verbal Learning Test (CVLT)-II 1–5 free recall		0.62	0.65
	A-A	0.63	0.62
	A-B	0.64	0.70
CVLT-II long-delay free recall		0.67	0.63
	A-A	0.58	0.82
	A-B	0.79	0.52

A-A, standard–standard; A-B, standard–alternate.

Practice Effects

A significant main effect of "group" (F [1, 74] = 6.58, P = 0.012) and "time" (F [1, 74] = 21.44, P < 0.0001) and a significant "type" × "time" interaction (F [1, 74] = 8.26, P = 0.005) were found on scores of the BACS List Learning (**Figure 2**). Accordingly, a secondary analysis was performed for each "type," which revealed a significant main effect of "time" in type A-A (F [1, 33] = 49.60, P < 0.0001), but not type A-B (F [1, 41] = 1.23, n.s.). As for the HVLT-R, there was a significant main effect of "group" (F [1, 74] = 10.05, P = 0.002), while "time" effect did not reach a significant level (F [1, 74] = 3.94, P = 0.051). A secondary analysis for each "group" revealed no significant main effect of "time" or "time" × "type" interaction in either healthy controls ("time": F [1, 40] = 0.84, n.s.; "time" × "type" interaction: F [1, 40] = 0.00, n.s.) or bipolar disorder patients ("time": F [1, 34] = 2.56, n.s.; "time" × "type" interaction: F [1, 34] = 2.90, P = 0.097). Repeated measures ANOVA for CVLT-II 1–5 Free Recall revealed a significant effect of "group" (F [1, 74] = 8.24, P = 0.005) and "time" (F [1, 74] = 27.97, P < 0.0001). "Type" × "time" interaction was also significant (F [1, 74] = 28.42, P < 0.0001). Therefore, secondary analysis for each "type" was performed. There was a significant effect of "time" in type A-A (F [1, 33] = 67.71, P < 0.0001), but not type A-B (F [1, 41] = 0.00, n.s.). In addition, "group" × "time" interaction was not significant in either "type" (type A-A: F [1, 33] = 0.02, n.s.; type A-B: F [1, 41] = 1.94, n.s.). As for CVLT-II Long-Delay Free Recall, "group" effect (F [1, 74] = 6.76, P = 0.011) and "time" effect (F [1, 74] = 11.47, P = 0.001), as well as "type" × "time" interaction (F [1, 74] = 4.68, P = 0.034) were significant. Also, "group" × "type" × "time" interaction was significant (F [1, 74] = 6.37, P = 0.014). A secondary analysis revealed a significant effect of "time" in type A-A (F [1, 33] = 17.21, P = 0.0002), but not type A-B (F [1, 41] = 0.72, n.s.). Moreover, "group" × "time" interaction was not significant in either pattern (type A-A: F [1, 33] = 2.87, n.s.; type A-B: F [1, 41] = 3.72, n.s.).

Criterion-Related Validity

The criterion-related validity of the CVLT-II 1–5 Free Recall and Long-Delay Free Recall tasks were examined using the HVLT-R Immediate Recall and BACS List Learning tasks in patients with

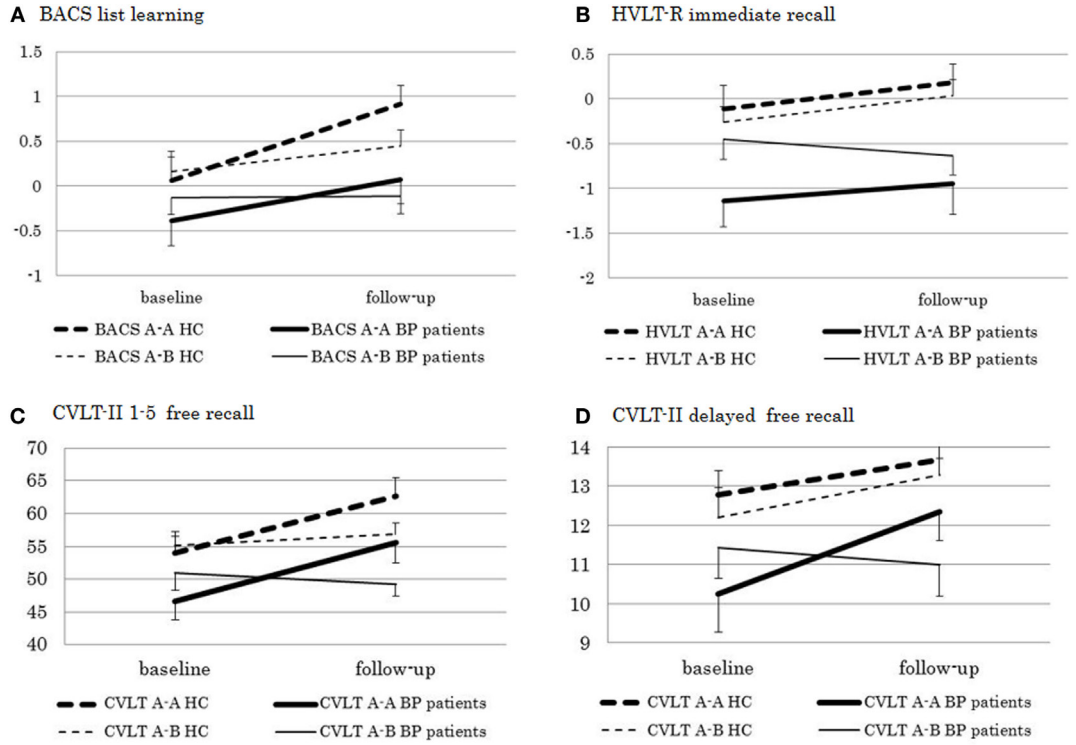

FIGURE 2 | Test–retest performance on **(A)** the Brief Assessment of Cognition in Schizophrenia (BACS) list learning and **(B)** HVLT-R immediate free recall (presented in *z*-score), and **(C)** CVLT-II 1–5 free recall and **(D)** delayed free recall (presented in raw score) in bipolar disorder patients and healthy controls. A-A, standard form–standard form pattern; A-B, standard form–alternate form pattern.

bipolar disorder. Pearson's product-moment correlation coefficients ranged from 0.68 to 0.81.

DISCUSSION

The CVLT-II Japanese version and HVLT-R, but not BACS were found to discriminate between bipolar disorder patients and healthy individuals with a sensitivity comparable to that of the HVLT-R. Strong correlations with performances on the BACS List Learning and HVLT-R Immediate Recall suggest a good criterion-related validity of the CVLT-II as a tool to detect cognitive disturbances in patients with bipolar disorder. There was no consistent relationship between mood symptoms and performance on the CVLT-II in the subsyndromal patients.

Between-Group Differences

Interestingly, between-group differences were significant in scores of the CVLT-II 1–5 Free Recall and Long-Delay Free Recall, and HVLT-R Immediate Recall, but not BACS List Learning. One of the reasons may be that the word lists in the CVLT-II and HVLT-R are semantically organized while this is not the case with the BACS. It may be that bipolar disorder patients show impairment in semantic clustering, in agreement with previous suggestions that the impairment in verbal organizational strategies causes the difficulty in recalling words (13, 29).

The patient–control effect size of the CVLT-II 1–5 Free Recall (0.52) was smaller than those previously reported using the CVLT (0.73–0.82) (4). Meanwhile, the effect size for the HVLT-R Immediate Recall (0.56) was slightly larger than that reported in Schretlen et al. (30) for bipolar disorder patients (0.42) (30). The overall performance on the CVLT-II 1–5 Free Recall at baseline (0.73 for the healthy controls and 0.65 for the bipolar disorder patients) were still worse than that in the HVLT-R Immediate Recall (0.76 and 0.69), suggesting a satisfactory level of cognitive demands of the CVLT-II.

Test–Retest Reliability and Practice Effect of Verbal Learning Measures

We found moderate to good test–retest reliability in both CVLT-II 1–5 Free Recall and Long-Delay Free Recall scores in bipolar disorder patients and healthy controls. In a previous investigation on the CVLT-II,[17] the reliability coefficients ranged from 0.72 to 0.79 in a sample of 288 healthy subjects, with a median interval of 21 days, similar to the ICC for the CVLT-II 1–5 free recall in healthy controls using an alternate form (0.70) in the present study (**Table 2**). Interestingly, the HVLT-R Immediate Recall generally showed greater ICC values than the other tests, attaining a good to excellent level.

Criterion-Related Validity

Both CVLT-II 1–5 Free Recall and Long-Delay Free Recall scores showed strong correlation with either the BACS List Learning or HVLT-R Immediate Recall scores, suggesting good criterion-related validity.

Relationship of Performance on the CVLT-II with Mood Symptoms

Meta-analytic studies generally report that bipolar patients with the more severe depressive or manic symptoms are likely to show the worse performance on tests of learning and memory [reviewed in Ref. (19)]. On the other hand, the lack of a significant relationship between manic symptoms, measured by the YMRS, and performance on the CVLT-II, reported here, may be related to the inclusion of subsyndromal patients. The *positive* correlations between ratings with the MADRS and CVLT-II scores, obtained in this study, seem somewhat contradictory and might be also due to the nature of the subjects studied.

Task-Specific Decline in Memory Performance in Bipolar Disorder

The CVLT-II is characterized by the (four category)/(four words per category) structure (26), while the HVLT-R consist of (three category)/(four words per category) (15). On the other hand, the BACS List Learning does not have such "internal category" structure. This difference may provide a major reason why only the former two tasks were able to discriminate between patients and control subjects. This concept may be partly supported by Deckersbach et al. (13), who found the contribution of memory organizational strategy to poor performance on the Long-Delay Free Recall Task of the CVLT. Further studies with data from other psychiatric conditions would help understand the nature of cognitive impairment of mood disorders.

Limitations

Unlike previous studies, patients with bipolar disorder studied here were not necessarily in the *euthymic* state, although all met the *subsyndromal* state criterion. There is a possibility that the patient-control effect sizes may have been overestimated due to residual depressive symptoms. However, a *positive* correlation between rating with the MADRS vs. CVLT-II 1–5 Free Recall and Long-Delay Free Recall scores may argue against this view.

CONCLUSION

The Japanese version of CVLT-II appeared to provide valid measures of verbal learning and memory function in bipolar disorder patients. The ability of the CVLT-II and HVLT-R, but not BACS List Learning, to discriminate between patients and control subjects may be related to the use of memory organization strategy specific to the CVLT-II and HVLT-R, which deserves further study.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of "name of guidelines, name of committee" with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by ethics committees of the National Center of Neurology and Psychiatry Hospital, Fujita Health University Hospital, Nagoya University Hospital, and Hokkaido University Hospital.

AUTHOR CONTRIBUTIONS

Contributions of each author are as follows: conception and design of the study (TS); acquisition of data (AT, NK, TK, IK, NO, and NI); analysis of data (KN and KS); and drafting of the manuscript (KN and TS).

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MINI REVIEW
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Competence to Consent and Its Relationship With Cognitive Function in Patients With Schizophrenia

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Decisional capacity to consent is an emerging ethical and legal concept, and is closely related to self-determination of patients facing important medical decisions or research participations. Recently, the MacArthur Competence Assessment Tool (MacCAT), a semi-structured interview consisting of four dimensions (Understanding, Appreciation, Reasoning, and Expression of a Choice), was developed to assess the decisional capacity. Decision-making capacity in a group of patients with schizophrenia, as measured by the MacCAT, has been shown to be impaired in comparison with healthy control people. However, this does not necessarily mean the presence of impaired decisional capacity in all cases. Considering the real-world practice of obtaining informed consent from patients with schizophrenia, it is important to evaluate the relationship between psychopathological features and decisional capacity of the illness. Negative symptoms of schizophrenia have been demonstrated to be related to the ability to understand information relevant to the decision, reason rationally, and appreciate a situation and its consequences. On the other hand, positive symptoms, such as delusions and hallucinations have been an inconsistent correlate of poor capacity. Furthermore, some studies indicate that impairment of cognitive function, a core symptom of schizophrenia, could be more largely associated with decisional capacity than positive and negative symptoms. Therefore, it is reasonable to assume cognitive enhancement would enlarge the capacity to consent and promote autonomy in medical treatment and research participation in patients with schizophrenia. Further studies are warranted to elucidate this and related issues.

Keywords: competence to consent, cognitive function, schizophrenia, MacArthur Competence Assessment Tools, decisional capacity

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INTRODUCTION

Competence to consent for individuals with psychiatric symptoms or impaired cognitive functioning has become central to the debate on the informed consent in clinical care and research settings. Clinicians and researchers bear the responsibilities to protect two aspects of human rights; the right of competent patients to make choices about their medical care and the right of incompetent patients to be protected from the potential harm of their decisions (1). However, in real-world clinical settings, some patients with capacity were detained in hospital by law, or other patients with incapacity were admitted to hospital on a voluntary basis (2). In terms of

clinical research, some patients with incapacity might have participated in clinical trials with their own consent.

Although several decision-making tasks specifically assess decisional capacities (3, 4), the medical/psychiatric literature has commonly cited the following abilities as relevant to capacity for informed consent: (1) understanding information relevant to treatment decision making; (2) appreciating the personal significance of treatment information, especially concerning one's own illness and the probable consequences of one's treatment options; (3) reasoning with relevant information to engage in a logical process of weighting treatment options; and (4) expressing a choice (5). These are also the key elements of the MacArthur Competence Assessment Tool (MacCAT) (6) (**Figure 1**), which has been widely used for competence assessment (7). However, the MacCAT is not clearly designed to provide a total score for the assessment of decision-making capacity. Furthermore, the abilities assessed in the MacCAT do not necessarily equate to the abilities relevant to the assessment of decision-making capacity in many jurisdictions.

Schizophrenia is a severe mental disorder that generally appears in late adolescence or early adulthood. Epidemiological data indicates that prevalence of schizophrenia is approximately 1% in the worldwide population. Symptoms of schizophrenia are clinically divided into three main categories of positive symptoms (delusions, disordered thoughts, and hallucinations), negative symptoms (restricted affect and drive), and impairments in cognitive function (8, 9). When schizophrenia was first identified by Kraepelin, he noted the fundamental role of cognitive impairment in this disorder, and called this dementia praecox (10). Although patients with schizophrenia are more likely to lack the competence to consent than control groups (6, 11), the diagnosis of schizophrenia cannot be equated with decisional incapacity (12). Many researchers have investigated the associations of competence to consent with positive and negative symptoms of schizophrenia (13–15). Although poor capacity has correlated with negative symptoms more consistently than positive symptoms, high levels of positive symptoms, including disorganization, may affect competence to consent. Furthermore, recent empirical data suggest that neurocognitive functioning could explain a larger proportion of the variance in competence to consent than positive and negative symptoms of schizophrenia (14, 16, 17).

Therefore, the aim of this narrative review is to elucidate (1) the relationships between cognitive function and competence to consent, and (2) the interventions to compensate the decision-making capacity in patients with schizophrenia.

COGNITIVE MEASURES OF MULTIPLE DOMAINS AND COMPETENCE TO CONSENT

Several studies investigated the association of competence to consent and cognitive measures such as the Mini-Mental State Examination (MMSE) (15, 17–19) and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (13, 16). On the whole, poor understanding subscales of MacCAT have been a more consistent correlate of poor cognitive functioning than have other subscales. However, all of above mentioned studies employed MacCAT-Clinical Research (MacCAT-CR) for assessing participants' decision-making abilities for clinical research. So, the potential range of understanding subscales being at least three times those of the other subscales might affect inconsistent results of other subscales.

A longitudinal assessment for capacity, in terms of understanding, was conducted among participants in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia study (20). Over 18 months treatment, poorer baseline neurocognitive composite scores consisting of processing speed, verbal memory, vigilance, reasoning, and working memory, predicted falling below the critical decision-making capacity threshold. In the same analysis, lower baseline scores of understanding subscale also were associated with falling below the threshold during follow-up period.

COGNITIVE MEASURES OF EACH DOMAIN AND COMPETENCE TO CONSENT

Verbal communication plays an important role in informed consent (21). Two studies demonstrated the relationship between understanding subscales and verbal cognitive functioning based on the Wechsler Adult Intelligence Scale (WAIS)-Revised (WAIS-R) (22, 23). In addition, other studies showed that appreciation and reasoning subscales are associated with verbal comprehension composed of vocabulary, similarities, and information subtests from the WAIS–Third Edition (WAIS-III) (17, 24). Although previous studies indicated that verbal abilities may predict competence to consent, the relationship between specific dimensions of decisional capacity and individual verbal ability areas is still obscure.

Memory is a complex process, consisting of registration, storage, retainment, and retrieval of information (25). Previous studies from US revealed that the RBANS memory index had significant relationships to understanding, appreciation (13) and reasoning subscales (16). Another study from Hong Kong indicated an association of understanding subscales with immediate and delayed logical memory from the Wechsler Memory Scale (WMS) (5). Furthermore, some studies implicated that memory also underlies an aspect of learning outcome (17, 24). Palmer et al. showed the relationship of learning composite scores with three subscales of MacCAT (understanding, appreciation, and reasoning) (24). They also demonstrated that auditory and visual learning abilities could affect the competence to consent (17).

Working memory is a complex and multifaced construct to store and simultaneously manipulate a limited amount of information during short intervals. This capacity facilitates further cognitive processing, such as response selection relevant for a specific context. Working memory comprises two short-term information storage systems, the visuospatial network for visual material and the phonologic loop for verbal-acoustic material (25). In the CATIE schizophrenia trial (14), this cognitive domain was assessed by a computerized test of

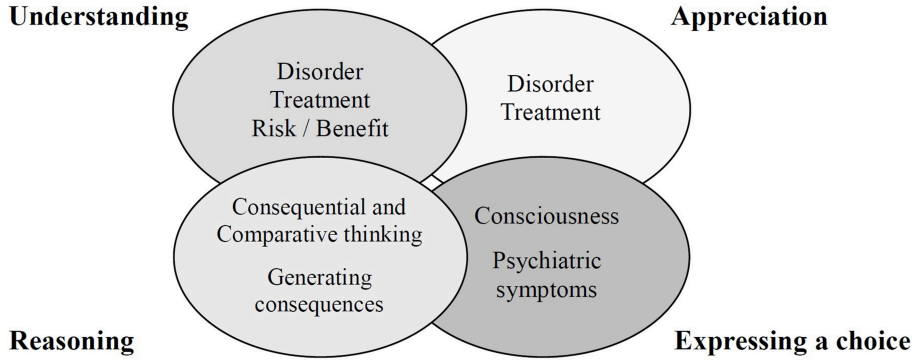

FIGURE 1 | Key elements of the MacArthur Competence Assessment Tool.

visuospatial working memory and letter number sequencing test of auditory working memory. Specifically, working memory performance showed considerable bivariate relationships with the understanding, appreciation, and reasoning subscale scores from the MacCAT-CR. Furthermore, similar results were reported in other studies employing the letter number sequencing test (5) and WAIS-III (17). A previous study indicated an association between language comprehension and working memory for sentences (26). Impairment of working memory in patients with schizophrenia might be consequent upon verbal comprehension deficits.

Information processing represents a cognitive process of taking information and encoding it to be understood and recalled when appropriately cued. Processing speed is the rapidity by which information processing occurs (25). Several studies showed bivariate correlation between processing speed composite scores and understanding, appreciation, and reasoning subscales of MacCAT (14, 17, 24), but only the relationship between processing speed composite scores and understanding subscales was replicated in a multiple regression model (14). In patients with schizophrenia, processing speed performance is strongly associated with global cognitive deficits (27). Thus, processing speed may contribute to the relationship between competence to consent and general cognitive performance.

Executive function involves the simultaneous use of information rather than the basic cognitive process, and governs goal-directed behaviors or adaptive responses to complex or novel situations. Generally, executive function is characterized by several complex mental abilities, including unique skills used for expansion, modulation, and implementation of goal-directed activities (25). This domain of cognitive function has been thought to rely on frontal lobe functions (28). A positive correlation has been reported between performance on the Frontal Assessment Battery and total scores of the MacCAT (29) in chronic schizophrenia patients. Specifically, scores on the understanding subscale were most consistently correlated with executive function (5, 24).

Cognitive underpinnings underlying the limited decisional capacity in psychiatric patients remain to be explored (30). One intriguing study (31) showed that performance on a metacognition test was more closely related to decisional capacity compared to executive function. Metacognition focuses on the level of self-confidence of patients in comparison with actual performance, and predicts performance on the MacCAT-T (31).

INTERVENTIONS TO COMPENSATE THE DECISION-MAKING CAPACITY

Although antipsychotic medication may improve decisional capacities (32, 33), clinicians and researchers should improve the informed consent process to maximize the decision-making capacities of patients with schizophrenia. Providing information repeatedly and discussing presented information with participants may strengthen the competence to consent (16, 34). Furthermore, consent procedures via multimedia may facilitate the understanding to decide on complex or high-risk protocols (35). Naughton et al. conducted a small uncontrolled study to evaluate the effect of metacognitive training (MCT) to improve a person's awareness of cognitive biases and thinking styles on decision-making capacities (36). MCT was found to elicit improvement in understanding and reasoning, but not appreciation abilities of patients. Furthermore, cognitive remediation may improve competence to consent (37), providing ethically adequate care, as well as clinical improvement.

LIMITATIONS

Several limitations of this review should be acknowledged. The principal limitation is the relatively small sample sizes in most studies, mentioned here, on the relationship between cognitive function and competence to consent in patients of schizophrenia. Secondly, for ethical and legal reasons, only subjects who consented to participate in studies were included. Even among individuals who consented to participate, 10% were too agitated to complete the entire assessments (6), suggesting that generalization of previous findings should be considered with caution. Thirdly, the MacCAT does not have a specific cutoff to dichotomize competence vs. incompetence. This

may obscure the associations between cognitive functions and decisional capacities (38). Finally, the MacCAT, which is based on not only medical literature but also existing case law and statutes, does not assess the emotional aspect of decisional capacities. Further studies investigating the relationship between cognitive function and decisional capacities, including both comprehensive emotional and legal aspects, are needed.

CONCLUSIONS

Neurocognitive functioning may explain competence to consent more accurately than positive and negative symptoms. Previous results have not indicated differential relationships between specific cognitive ability areas and decision-making capacity. Interventions with multimedia procedure, MCT, etc. likely enhance competence to consent. Cognitive remediation might provide ethically adequate care as well as clinical improvement. Clinicians and researchers are responsible for maximizing decision-making capacities of patients in the informed consent process. Further studies are warranted to elucidate competence to consent and related issues.

AUTHOR CONTRIBUTIONS

NS, NY-F, and TS were involved in the study concept, interpretation of manuscript, critical revision of manuscript for intellectual content, literature review, and drafting of the manuscript.

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REVIEW
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Medications Used for Cognitive Enhancement in Patients With Schizophrenia, Bipolar Disorder, Alzheimer's Disease, and Parkinson's Disease

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Background/aims: Cognitive impairment, which frequently occurs in patients with schizophrenia, bipolar disorder, Alzheimer's disease, and Parkinson's disease, has a significant impact on the daily lives of both patients and their family. Furthermore, since the medications used for cognitive enhancement have limited efficacy, the issue of cognitive enhancement still remains a clinically unsolved challenge.

Sampling and methods: We reviewed the clinical studies (published between 2007 and 2017) that focused on the efficacy of medications used for enhancing cognition in patients with schizophrenia, bipolar disorder, Alzheimer's disease, and Parkinson's disease.

Results: Acetylcholinesterase inhibitors and memantine are the standard treatments for Alzheimer's disease and Parkinson's disease. Some studies have reported selective cognitive improvement in patients with schizophrenia following galantamine treatment. Newer antipsychotics, including paliperidone, lurasidone, aripiprazole, ziprasidone, and BL-1020, have also been reported to exert cognitive benefits in patients with schizophrenia. Dopaminergic medications were found to improve language function in patients with Parkinson's disease. However, no beneficial effects on cognitive function were observed with dopamine agonists in patients with schizophrenia. The efficacies of nicotine and its receptor modulators in cognitive improvement remain controversial, with the majority of studies showing that varenicline significantly improved the cognitive function in schizophrenic patients. Several studies have reported that *N*-methyl-D-aspartate glutamate receptor (NMDAR) enhancers improved the cognitive function in patients with chronic schizophrenia. NMDAR enhancers might also have cognitive benefits in patients with Alzheimer's disease or Parkinson's disease. Raloxifene, a selective estrogen receptor modulator, has also been demonstrated to have beneficial effects on attention, processing speed, and memory in female patients with schizophrenia.

Conclusion: Clinical trials with larger sample sizes evaluating comprehensive cognitive domains are warranted to examine the efficacy of medications in cognitive enhancement in patients with schizophrenia, bipolar disorder, Alzheimer's disease, and Parkinson's disease.

Keywords: cognitive impairment, medication, schizophrenia, bipolar disorder, Alzheimer's disease, Parkinson's disease

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INTRODUCTION

Cognitive function, including neurocognition and social cognition, is associated with mental processes that lead to the acquisition of information and knowledge. It drives an individual's understanding and actions in his or her environment. Neurocognition and social cognition can predict the functional outcome in an individual with schizophrenia or bipolar disorder (1). Normal cognitive changes generally occur with aging, such as the decline in processing speed, memory, language, and visuospatial and executive function abilities (2). Therefore, elderly people require longer time to learn and recall information (3).

Cognitive impairment is the frequent symptom occurring in nonelderly patients with schizophrenia or other neurodegenerative disorders (4). Cognitive dysfunction in patients with schizophrenia was described by Kraepelin more than a century ago (5). Increased awareness and advancements in the area of neuropsychological assessment and neuroimaging techniques have now rendered cognitive impairment an important focus of theories on the etiology and treatment of schizophrenia.

A large-scale comprehensive quantitative meta-analysis study reported that patients with schizophrenia have moderately to severely impaired neurocognition, particularly in terms of global verbal memory functioning (6). Furthermore, multiple analyses in the Clinical Antipsychotic Trials of Intervention Effectiveness study on schizophrenia have suggested that patients with schizophrenia are characterized by a broad cognitive deficit (7). Another meta-analysis study reported that deficits across multiple social cognitive domains in patients with schizophrenia were clear and replicated, particularly in the domains of theory of mind (ToM) and emotion perception (8). Patients with schizophrenia are impaired in various cognitive functions, including both neurocognition and social cognition, which are associated with a functional outcome. Neurocognitive function was also found to be impaired in euthymic patients with bipolar disorder (9). In addition, a meta-analysis of patients with bipolar disorder in the euthymic stage reported the presence of deficits in emotion processing and ToM (10). Patients with bipolar disorder are also impaired in both neurocognition and social cognition. Moreover, neurocognitive impairment has been found to be similar among patients with bipolar disorder and patients with schizophrenia (11).

Mild cognitive impairment (MCI) and dementia are not a part of the normal aging process. MCI has been defined as a greater decline in cognition without significant daily life interference than that in normal aging considering the education and the age of an individual (12). In individuals with dementia, these symptoms involve mental decline that is sufficiently severe to disrupt their daily life activities (13).

The mechanisms of cognitive impairment are different among patients with schizophrenia, bipolar disorder, Alzheimer's dementia, and Parkinson's disease. Schizophrenia is a complex disorder. Cognitive deficit has been considered as one of the core symptoms of schizophrenia (14–16). The deficiency in proactive control is directly related to the impairment in the dorsolateral prefrontal cortex (DLPFC). This impairment might be related to DLPFC dysfunction; impaired DLPFC connectivity with the striatum, the thalamus, and the parietal cortex; and alterations in the levels of neurotransmitters, including glutamate, γ-aminobutyric acid (GABA), and dopamine (17). The mechanism of cognitive impairment in patients with bipolar disorder has not yet been clearly elucidated. Some researchers believe that cognitive decline is linked with the mechanisms of neuroinflammation and neuroprotection in bipolar disorder (18). Alzheimer's disease, a neurodegenerative disease with a progressive course, is characterized by two specific lesions, extracellular β-amyloid plaques and neurofibrillary tangles (19–21). The glutamate system has also been reported to play a crucial role in cognitive function (22). Synaptic dysfunction in Alzheimer's disease has been presumed to be related to glutamate receptors. Synaptic transmission and synaptic plasticity can be damaged by the β-amyloid protein. Metabotropic and *N*-methyl-D-aspartate glutamate receptors (NMDARs) have also been reported to be involved in Alzheimer's disease (23). Cognitive deterioration in patients with Parkinson's disease occurs due to the dysmetabolism of both amyloid protein and α-synuclein and cholinergic dysfunction (24, 25).

As mentioned earlier, although the mechanisms of cognitive impairment vary among different neurodegenerative disorders, cognitive impairment has been currently regarded as an important determinant of functional domains and is a potential treatment goal in patients with schizophrenia, bipolar disorder, Alzheimer's disease, and Parkinson's disease.

Cognitive enhancement still remains a clinically unresolved challenge. Till date, there is no effective treatment available for enhancing cognitive function in patients with schizophrenia, bipolar disorder, Alzheimer's disease, and Parkinson's disease. This review article systemically examines and presents an update on pharmacological cognitive enhancement in patients with schizophrenia, bipolar disorder, Alzheimer's disease, and Parkinson's disease.

METHOD OF REVIEW

We performed a search of studies related to our topic using PubMed Clinical Queries in July 2017. We searched for human clinical trials focusing on cognitive enhancement in patients with schizophrenia, bipolar disorder, Alzheimer's disease, and Parkinson's disease, excluding other cognitive disorders. The following search string was used: "(Cognitive function OR Cognitive enhancer OR Cognition improvement) AND medication AND (Schizophrenia OR Bipolar disorder OR Alzheimer disease OR Parkinson's disease)." We limited the search results to articles

Abbreviations: CATIE, clinical antipsychotic trials of intervention effectiveness; ToM, theory of mind; MCI, mild cognitive impairment; DLPFC, dorsolateral prefrontal cortex; GABA, glutamate, γ-aminobutyric acid; NMDARs, *N*-methyl-D-aspartate glutamate receptors; FDA, Food and Drug Administration; ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; MMSE, Mini-Mental State Examination; FAB, frontal assessment battery; MoCA, Montreal Cognitive Assessment; RLAI, risperidone long-acting injection; BACS, Brief Assessment of Cognition in Schizophrenia score; PP, paliperidone palmitate long-acting injection; CVLT, California Verbal Learning Test; MATRICS, measurement and treatment research to improve cognition in schizophrenia; MoCA-J, MoCA-Japanese version; GMLT, Groton Maze Learning Task; DAAO, D-amino acid oxidase; EPO, erythropoietin; DHEA, dehydroepiandrosterone; DHEAS, DHEA sulfated form.

published between January 1, 2007, and June 30, 2017, and those with "clinical trial" as the article type, which resulted in a total of 799 articles. We excluded the string "Alzheimer's disease OR dementia" from our search due to the availability of several lines of evidence indicating treatment efficacy and US Food and Drug Administration (FDA) approval (26–28). Several compounds for enhancing cognition in patients with schizophrenia and degenerative diseases were reported in the retrieved articles. We review and summarize these clinical trials in the present article.

ACETYLCHOLINESTERASE INHIBITORS

Three acetylcholinesterase inhibitors, donepezil, galantamine, and rivastigmine, have been approved by the US FDA for treating Alzheimer's disease (29–31). Treatment with acetylcholinesterase inhibitors resulted in higher concentrations of acetylcholine, leading to the inhibition of aggregation of β-amyloid and increased communication between neurons, which in turn decreases cognitive decline (13).

A total of 11 clinical trials pertained to treatment with acetylcholinesterase inhibitors for improving cognitive function in patients with schizophrenia, which included five studies on galantamine, four studies on donepezil, and one study each on rivastigmine and neuromidin (32–42). All the five small-sample, randomized, double-blind, placebo-controlled studies on galantamine adjunctive treatment reported no beneficial effects on cognitive function in the galantamine-treated patients with schizophrenia (32–36). Among the four clinical studies on donepezil adjunctive treatment, three randomized, double-blind, placebo-controlled trials reported no significant improvement in neurocognitive function in the donepezil-treated patients with schizophrenia (37–39). The other open-label trial showed that donepezil adjunctive treatment in stable schizophrenic patients resulted in significant improvement in mental set-shifting ability ($p < 0.05$), long-term memory and learning ability ($p < 0.05$), and attention ($p < 0.05$) among 13 patients (40). The randomized crossover design study on rivastigmine adjunctive therapy reported no significant cognitive improvement in the rivastigmine-treated patients (41). Finally, the randomized controlled study on neuromidin, a nonselective acetylcholinesterase inhibitor, evaluated 55 marked neurocognitive deficits in patients with schizophrenia and demonstrated positive improvement in visuospatial memory, attention, retention and retrieval of data, and planning (42). Thus, the majority of these clinical studies have demonstrated no significant improvement in neurocognitive function in patients with schizophrenia treated with acetylcholinesterase inhibitors.

Three clinical trials pertained to treatment with acetylcholinesterase inhibitors for enhancing cognition in patients with bipolar I disorder (43–45). Iosifescu et al. (43) administered galantamine ER 8–24 mg daily to patients with bipolar disorder for 4 months in an open-label study. After treatment, these patients showed obvious improvement in verbal episodic memory ($p < 0.05$), attention ($p < 0.05$), and subjective cognitive scores ($p < 0.01$) (43). Gildengers et al. (44) conducted a small-scale, 12-week, open-label pilot study in elderly patients with bipolar I or II disorder. They observed that acute treatment with donepezil (5–10 mg/day) was not related to amelioration of cognition and daily life activities. Ghaemi et al. (45) performed a double-blind, placebo-controlled study to investigate the cognition efficacy of galantamine augmentation in patients with euthymic bipolar disorder. They reported improvement in California Verbal Learning Test (CVLT) Total Learning in the galantamine group from baseline and improvement in the category fluency and the Delis–Kaplan executive function system trail-making conditions in the placebo group from baseline. There was no significant difference between galantamine and placebo groups possibly due to small sample size. Hence, the efficacy of acetylcholinesterase inhibitors on cognition in patients with bipolar disorder remains uncertain due to the concerns of placebo effect, limited sample size, and the inconsistent results of previous studies. Further trials with larger sample sizes addressing the concern of placebo effect are warranted.

Five clinical studies evaluated the efficacies of acetylcholinesterase inhibitors on cognition in patients with Parkinson's disease, which included two clinical trials on galantamine and two on rivastigmine.

A small-sample, open-label, controlled trial on patients with Parkinson's dementia who received galantamine demonstrated higher scores on the Mini-Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog), frontal assessment battery (FAB), and clock drawing test than those in the control group at the end of the study (46). Another double-blind, placebo-controlled study did not find improvement in visuospatial performance, memory, or attention/execution in patients who received galantamine treatment among those with nondemented Parkinson's disease (47). Both clinical trials demonstrate the lack of evidence to confirm the cognitive benefits of galantamine in patients with Parkinson's disease.

A small-sample, 24-week, randomized, double-blind, placebo-controlled, crossover, single-site study of MCI in patients with Parkinson's disease demonstrated a significant effect of rivastigmine transdermal patch in terms of the Everyday Cognition Battery Memory Test ($p < 0.05$); in contrast, no treatment effect was found in terms of Dementia Rating Scale-2, Montreal Cognitive Assessment (MoCA), and NeuroTrax Computerized Cognitive Battery scores (48). Another 12-month observation study involving patients with Parkinson's disease having cognitive dysfunction reported that patients treated with rivastigmine showed significantly greater improvement in MoCA scores ($p < 0.01$) than that of the controls (49). Both clinical trials have demonstrated the evidence of cognitive benefits in patients with Parkinson's disease and cognitive impairment treated with rivastigmine.

Thus, the majority of clinical studies have demonstrated significant efficacy of acetylcholinesterase inhibitor, rivastigmine, in Parkinson's disease patients with MCI or dementia. These trials did not show effectiveness of acetylcholinesterase inhibitor on cognition in patients with Parkinson's disease. To gain generalizability, further large-scale double blinded trials are warranted.

MEMANTINE

Memantine, an antagonist of NMDARs, has been approved by the US FDA for treating moderate-to-severe Alzheimer's disease (50). It has been reported that memantine could provide both

neuroprotection and symptomatic improvement through rapid, moderate-affinity, voltage-dependent NMDAR channel blockade (51). It also has favorable effects on cognitive impairment in other neurodegenerative diseases. We identified seven clinical studies that evaluated the efficacy of memantine treatment on cognitive function in schizophrenic patients in our search. In three of these studies, a 6-week, open-label study; an 8-week, double-blind, placebo-controlled study; and a 12-week, placebo-controlled study, memantine (adjunctive therapy) showed no efficacy on cognition improvement (52–54). However, in the other 12-week, small-sample with 21 patients, double-blind, placebo-controlled study, patients with refractory schizophrenia who were treated with memantine showed a significantly greater MMSE improvement ($p < 0.01$) than the improvement of those who received placebo (55). A 26-week, randomized, double-blind, placebo-controlled crossover study also demonstrated the efficacy of memantine on cognitive function, with a composite memory score comprising verbal recognition memory and paired associates learning task scores on the Cambridge Neuropsychological Test Automated Battery (effect size = 0.30, $p < 0.05$), in 52 clozapine-refractory schizophrenic patients (56). However, the continued open-label 1-year extension study did not show the cognitive benefit at weeks 26 and 52 (57). Another 12-week, randomized, double-blind, placebo-controlled clinical trial also reported significant improvement in the MMSE score in the memantine intervention group at week 6 ($p < 0.05$) and week 12 ($p < 0.01$) in patients with schizophrenia treated with risperidone (58). Although some of the aforementioned studies have reported positive effects of memantine intervention on cognitive function, the results were inconsistent possibly due to the variations in treatment duration. Thus, the effect of memantine on cognitive impairment in patients with schizophrenia remains uncertain. Further double-blind, placebo-controlled trials with longer treatment duration are needed to determine the efficacy of memantine on cognitive impairment in patients with schizophrenia.

We did not find any clinical trial on the effect of memantine on cognitive enhancement in patients with bipolar I disorder in our search. However, we identified one clinical study evaluating the effect of memantine on cognition in patients with Parkinson's disease complicated by dementia. This small-sample, long-term, open-label, controlled trial showed that patients with Parkinson's disease who received memantine exhibited significant improvement in the MMSE ($p < 0.05$), ADAS-cog ($p < 0.05$), clock drawing test ($p < 0.05$), and FAB scores ($p < 0.01$), compared to that in the controls at week 24 (59). At the end of 52 weeks, significant changes were observed in the 12-item Neuropsychiatric Inventory scale scores compared to those at baseline in the memantine-treated patients ($p < 0.05$) (59). This clinical trial showed that memantine appeared to be effective on cognition. The effects of memantine on cognition in Parkinson's disease have not yet been established because of the open-label study design and small sample size. Hence, further well-designed, double-blind, placebo-controlled trials with larger sample sizes are required to determine the efficacy of memantine on cognitive impairment in patients with Parkinson's disease.

ANTIPSYCHOTICS

Antipsychotics are the major medications for schizophrenia or psychosis for controlling psychotic symptoms. In addition to psychotic symptoms, extensive evidence indicates the presence of cognitive impairment accompanying schizophrenia. The cognitive efficacy of antipsychotics has gained more research attention in the recent 10 years. Several clinical trials on second-generation antipsychotics have focused on cognition in patients with schizophrenia.

In a 24-week, non-randomized, open-label trial, the mean change in Wisconsin Card Sorting Test Keio Version in the number of categories achieved ($p < 0.05$) and the perseverative errors in Nelson ($p < 0.05$) from baseline at the second stage was found to be significantly greater in the risperidone long-acting injection (RLAI) group than that in haloperidol decanoate depot group (60). The mean changes from baseline in the individual St. Marianna University School of Medicine's Computerized Memory Test, including immediate verbal recall ($p < 0.01$), delayed verbal recall ($p < 0.01$), delayed verbal recognition ($p < 0.01$), memory scanning test ($p < 0.05$), and memory filtering test ($p < 0.05$), were found to be significantly greater in the group switched to RLAI than those in haloperidol decanoate depot group (60). In a 6-month, open-label, randomized, controlled study, 30 patients with schizophrenia who were treated with RLAI were randomly allocated to the RLAI-continued group or the paliperidone palmitate long-acting injection (PP) group. The Brief Assessment of Cognition in Schizophrenia score (BACS) assessing the attention and processing speed item showed greater improvement in the PP group than that in the RLAI group ($p < 0.05$) (61). Another 12-week, small-sample, open-label study reported that the mean change from baseline in the z-score of the digit sequencing task was significantly improved after switching from risperidone to paliperidone in elderly schizophrenic patients (62). Furthermore, a 12-week, randomized, open-label study on schizophrenic patients demonstrated significantly greater improvements in recall after an interference phase in the verbal learning test in the paliperidone-switch group than those in the risperidone-continuation group, but not in the other six neurocognitive domains measured (63). A 6-week, placebo- and active-controlled study followed by a 6-month double-blind extension trial indicated that lurasidone 160 mg daily was superior to both placebo and quetiapine in terms of the neurocognitive composite at week 6 ($p < 0.05$), whereas there was no difference among lurasidone 80 mg daily, quetiapine XR 600 mg daily, and placebo. In the double-blind extension study, the lurasidone (40–160 mg daily) group showed significantly better cognitive performance than that in the quetiapine XR (200–800 mg daily) group at 6 months ($p < 0.01$) (64). Patients who received final doses of lurasidone 120 and 160 mg daily showed significantly greater improvement in the overall cognitive performance compared to that with quetiapine XR at 6 months, while 40 and 80 mg daily treatment showed a trend toward significance at 6 months (65). A 16-week, randomized, double-blind, placebo-controlled trial reported that adding ziprasidone to clozapine in patients with schizophrenia significantly improved semantic fluency ($p < 0.01$) (66). Another 18-week, randomized, double-blind trial

that compared clozapine and ziprasidone showed improvement in the composite cognitive score from baseline in both groups, although the improvements were significantly greater in the ziprasidone-treated group ($p < 0.05$) (67). A prospective, 12-week, multicenter, noncomparative, open-label study of aripiprazole in schizophrenic patients showed a significant improvement in verbal cognition from week 4 in terms of the long-term free recall in the CVLT over the scheduled visits in the trial ($p < 0.01$) and a significant improvement in phonemic (letter) subtest of the verbal fluency test from baseline to week 12 ($p < 0.05$) (68).

BL-1020, a new GABA-enhanced antipsychotic compound, 20–30 mg daily demonstrated significantly greater improvements in cognitive functioning as measured by the BACS composite score when compared to those with placebo ($p < 0.01$), risperidone 2–8 mg daily ($p < 0.05$), and BL-1020 10 mg daily ($p < 0.05$) after 6 weeks in a 6-week, randomized, double-blind, controlled trial (69). These clinical trials support the importance of cognitive improvement in patients with schizophrenia as a new focus of antipsychotic treatment. To summarize the efficacy on cognition, RLAI may be more effective than haloperidol decanoate depot, PP may be more effective than RLAI, lurasidone may be more effective than quetiapine XR, ziprasidone may be more effective than clozapine, and BL-1020 seems to be more effective than placebo from current clinical trials.

We did not find any clinical trial on antipsychotics for improving cognition in patients with bipolar disorder, Alzheimer's disease, or Parkinson's disease.

DOPAMINE AGONISTS AND AGENTS FOR ENHANCING DOPAMINE ACTIVITY

Dopamine, a brain catecholamine originating from subcortical neurons, has been reported to supplement the activity of several neural circuitries belonging to both subcortical and neocortical structures (70). However, the dopamine hypothesis of schizophrenia suggests that dopamine agonist medication supposedly worsens the positive symptoms of schizophrenia (71). The D2-selective blockade by antipsychotics has provided strong support for the dopamine hypothesis. However, the roles of other dopamine receptors in schizophrenia remain unclear. D1 and D2 receptors have been reported to exert opposing actions on intracellular signaling molecules and often have different physiological effects (72). It is well known that the D1 receptors of the prefrontal cortex are involved in working memory (73). D3 receptors are predominantly found in the limbic regions that modulate memory, emotions, and motivation (74). The D3 receptors are presumed to be associated with cognitive functioning. In our search, we identified only few articles pertaining to the effect of dopamine agonists on cognitive enhancement in schizophrenia. In a randomized controlled trial, pramipexole, a dopamine D3 agonist, was added for up to 12 weeks to ongoing antipsychotic treatment (75). The trial found no differences in cognition between the pramipexole and the placebo groups (75). In another randomized controlled trial of DAR-0100A, a dopamine-1 receptor agonist, 3 weeks of intermittent treatment with 0.5 or 15 mg or placebo showed no significant treatment effects on working memory domains of the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) (76). Thus, there is a lack of evidence to support the efficacy of dopamine agonists or agents for cognitive enhancement in patients with schizophrenia.

Regarding bipolar disorder, we found only one clinical trial on a dopamine agonist that increases dopamine activity for cognition enhancement. An 8-week, double-blind, placebo-controlled trial involving 35 euthymic patients subgroup with bipolar disorder demonstrated a significant improvement by treatment with pramipexole, an agonist for the D2, D3, and D4 dopamine receptors, in terms of the WAIS Digits Backward ($p < 0.05$) and Stroop Color Word tests ($p < 0.05$) (77). Due to the small sample and the short duration in this study, the evidence of dopamine agonists for cognitive enhancement in patients with bipolar disorder is limited.

However, we did not find any study on dopamine agonists for cognitive enhancement in patients with dementia in our search. Dopamine agonists represent a valid therapeutic option in Parkinson's disease. However, the efficacy of dopamine agonists on cognitive function in Parkinson's disease has not been well studied. In a randomized crossover study, rotigotine, cabergoline, nor levodopa improved cognition in 40 patients with early, mild Parkinson's disease compared to that in the off-treatment group (78). An open-label study reported that cognitive improvements as assessed by the MoCA-Japanese version (MoCA-J) total score and the subscore of delayed recall were found with 4–7 months of dopaminergic medication (L-dopa, a dopamine agonist, selegiline) treatment among 27 drug-naive patients with Parkinson's disease (79). Thus, the effect of dopamine agonists on cognition in Parkinson's disease remains uncertain due to the limitation in study design (only one randomized crossover study and one open-label study) and the small sample size.

Due to the limited clinical trials on the medications of dopamine activity enhancement found in our search, further well-designed clinical trials on dopamine-related medications, especially D1 and D3 agonists, for cognitive enhancement are still needed.

NICOTINE AND ITS RECEPTOR MODULATORS

A large body of evidence derived from studies supports the notion that nicotine has cognitive-enhancing effects. Several clinical studies have investigated the effects of nicotine and relative medications on cognitive function in patients with schizophrenia. In a randomized, placebo-controlled, crossover design study, 28 schizophrenic and 32 healthy nonsmokers received transdermal nicotine (14 mg/24 h) or a placebo patch (80). It was observed that nicotine had beneficial effects on attention in both schizophrenic and healthy nonsmokers, with intermediate performance by *ad libitum* smoking (80). Nicotine was related to a greater improvement in the inhibition of impulsive responses in patients with schizophrenia 3 h after each patch application (80). Another double-blind, randomized, placebo-controlled, crossover, 3-day pilot trial investigated the efficacy of intravenous nicotine on symptomatology and cognition in schizophrenic patients and reported no significant dose × time effects on the

Stroop Color-Word Test and continuous performance task (81). The efficacy of nicotine on cognition in patients with schizophrenia is still controversial based on both the aforementioned studies. Further well-designed, larger sample size, longer duration, double-blind, placebo-controlled trials are required to determine the efficacy of nicotine on cognition in patients with schizophrenia.

Varenicline, a partial agonist at the α4β2 receptor and also a full agonist at the α7 nicotine acetylcholine receptor, demonstrated significant improvement in several cognition domains related to verbal learning and memory, but not in domains related to attention or visuospatial learning or memory in a 6- to 9-week open-label study (82). However, a randomized, double-blind, placebo-controlled, 8-week study reported that varenicline showed significant improvement in nonperseverative errors in the Digital Symbol Substitution Test ($p < 0.05$) and the Wisconsin Card Sorting Test ($p < 0.05$) in subjects with schizophrenia (83). Varenicline was found to significantly reduce the Stroop Interference ($p < 0.01$) and the Continuous Performance Test hit reaction time ($p < 0.01$) compared to that with placebo among smokers but not among nonsmokers (83). In a phase 2, multicenter, double-blind, randomized, placebo-controlled trial involving patients with stable schizophrenia, AZD3480, another selective agonist of α4β2 and α2β2 nicotinic receptors, failed to improve cognition relative to placebo (84). These studies have thus reported the efficacy of varenicline on cognition improvement in patients with schizophrenia.

Encenicline is a novel selective α7 nicotinic acetylcholine receptor agonist. In a phase 2, 12-week, double-blind, randomized, placebo-controlled, parallel-design study, schizophrenic patients were randomized to receive either encenicline 0.27 or 0.9 mg or placebo daily (85). Patients who received 0.27 mg encenicline daily showed better Overall Cognition Index from the CogState computerized battery ($p < 0.05$) than that of patients who received placebo (85). Patients who received 0.9 mg encenicline daily showed greater improvement in Schizophrenia Cognition Rating Scale ($p < 0.05$) and in the Positive and Negative Syndrome Scale cognition domain ($p < 0.01$) compared to those in patients who received placebo (85). Another 12-week, randomized exploratory trial of an α7 nicotinic receptor agonist (TC-5619) demonstrated that TC-5619 led to significant improvement in Groton Maze Learning Task (GMLT; executive function) of the CogState Schizophrenia Battery ($p < 0.05$) at week 4 in patients with schizophrenia, but not at weeks 8 and 12 (86). However, TC-5619 led to significant improvement in GMLT at weeks 4 and 12 in the tobacco-use subgroup as well (86). A yet another phase 2, 24-week, randomized, double-blind study on patients with schizophrenia demonstrated that TC-5619 did not support a benefit for cognitive impairment (87). RG3487, an α7 nicotinic acetylcholine receptor partial agonist was reported to show no improvement in cognitive impairment in an 8-week, double-blind, randomized study on patients with schizophrenia (88). Thus, only encenicline demonstrated cognitive benefits in patients with schizophrenia patients in these clinical trials on α7 nicotinic receptor agonists.

We did not identify any clinical study evaluating the efficacy of nicotine and relative medications on cognition in patients with bipolar disorder in our search; however, we found two studies evaluating the effect of nicotine or relative medication in patients with Alzheimer's disease and Parkinson's disease. One was a phase 2, 12-week, double-blind, placebo-controlled study that reported that neither AZD3480 nor donepezil was significantly superior to placebo in terms of ADAS-Cog in patients with mild to moderate Alzheimer's disease (89). The other was a double-blind, placebo-controlled, crossover design study in which acute transdermal nicotine patches (7 mg for 24 h) were found to improve impaired controlled semantic processing ($p < 0.001$) in patients with Parkinson's disease (90). Nevertheless, due to the small sample size and the short duration of these trials, further well-designed trials with a larger sample size and a longer duration are needed to determine the efficacy of nicotine on cognition in patients with Parkinson's disease.

N-METHYL-D-ASPARTATE RECEPTOR ENHANCERS

N-methyl-D-aspartate glutamate receptors play an important role in learning and memory *via* neural plasticity, including long-term depression and potentiation. We identified five clinical studies evaluating the cognitive efficacy of NMDAR enhancers, including D-cycloserine, D-serine, sodium benzoate, sildenafil, and L-carnosine, in patients with schizophrenia in our search.

A 16-week, randomized, double-blind, double-dummy, parallel trial of adjuvant D-cycloserine, glycine, or placebo reported that glycine or D-cycloserine was not better than placebo in terms of cognitive performance (91). In another randomized, double-blind, parallel-group, 8-week trial, add-on D-cycloserine 50 mg administered once-weekly showed no improvement in cognitive performance compared to that with placebo (92). In a 4-week, open-label study, there was no obvious change in MATRICS for a D-serine dose of 30 mg/kg; however, improvement with a large effect size in MATRICS was observed for D-serine 60 mg/kg ($p < 0.01$) or more, suggesting a dose-dependent effect (93). D-Serine doses of 60 mg/kg or more led to a significant change across all domains, except working memory (93).

D-Amino acid oxidase (DAAO), a flavoenzyme of peroxisomes, can metabolize D-serine and D-alanine and exists in the central nervous system. Sodium benzoate, a DAAO inhibitor, enhances NMDAR function by inhibiting DAAO activity and increases the levels of D-amino acids. In a randomized, double-blind, placebo-controlled, 6-week study of 1 g daily sodium benzoate or placebo as an adjunctive to antipsychotics in patients with stabilized chronic schizophrenia, the benzoate group showed better performance than the placebo group in terms of processing speed ($p < 0.05$) and visual learning and memory ($p < 0.05$) (94).

Regarding sildenafil, a phosphodiesterase-5 inhibitor, Goff et al. (95) reported that it could increase the concentrations of cyclic guanosine monophosphate operated by NMDARs intracellularly, which has been presumed to be linked to memory consolidation and long-term potentiation. They administered a single oral dosage of sildenafil 50 or 100 mg or placebo in a randomized manner during a 48-h interval between prescriptions to 17 adult outpatients with schizophrenia who were under stable

antipsychotic treatment; however, neither dosage of sildenafil showed any significant impact on cognitive performance compared to that with placebo.

L-Carnosine, an antioxidant and antiglycation agent, has been shown to exert protective effects on cultured neurons against the deprivation of oxygen and glucose and NMDA-related neurotoxicity. Furthermore, studies have reported that it can reduce glutamate excitotoxicity effect in wild-type and histidine-decarboxylase-knockout mice (96, 97). In a 3-month, double-blind study, 75 symptomatically stable patients with chronic schizophrenia were assigned to receive either adjuvant L-carnosine 2 g daily or placebo randomly (98). Patients who received L-carnosine showed better performance in nonreversal set-shifting test than that of patients who received placebo; however, there was no significant difference in reversal reaction times and errors between the two groups (98). In addition, patients who received L-carnosine displayed better strategic efficiency ($p < 0.05$) with less perseverative errors ($p < 0.05$) than that of the control group (98).

Therefore, our search for NMDAR enhancers suggests that D-serine, sodium benzoate, and L-carnosine showed possible benefits on cognition in patients with schiozophrenia.

Regarding the enhancing effect of NMDARs on cognition in patients with Alzheimer's disease, a randomized, double-blind, placebo-controlled, 24-week trial demonstrated that patients with early-phase Alzheimer's disease who received sodium benzoate exhibited a greater improvement in ADAS-cog ($p = 0.0021$, 16 weeks; $p = 0.0116$, 24 weeks; $p = 0.0031$, end point) and additional cognitive score ($p = 0.007$ at end point) compared to the improvement of those patients who received placebo (99).

We identified another clinical study that evaluated the efficacy of NMDAR enhancers on cognitive function in patients with Parkinson's disease. This 8-week, double-blind, placebo-controlled trial showed that sarcosine, an NMDAR coagonist, did not show significant improvement in Cognitive Abilities Screening Instrument and MMSE scores compared to placebo (100).

However, we did not find any clinical trial on the efficacies of NMDAR enhancers on cognitive function in patients with bipolar disorder in our search.

ERYTHROPOIETIN (EPO)

Erythropoietin regulates red blood cell production or erythropoiesis. EPO improves oxygen capacity in the blood by boosting red blood cell production. Several animal model and cell studies have demonstrated that EPO exhibits a neuroprotective effect through antioxidant, antiapoptotic, anti-inflammatory, neurotrophic, angiogenic, and synaptogenic activities (101–103). In our search, we identified four clinical trials that evaluated the effect of EPO treatment on cognitive functions.

In a multicenter, randomized, double-blind, placebo-controlled, 12-week, phase II trial, patients with schizophrenia who received 40,000 IU recombinant human EPO for 3 months with a weekly short (15 min) intravenous infusion were found to experience a significant benefit compared to that of controls in cognitive test package, including Repeatable Battery for the Assessment of Neuropsychological Status subtests (delayed memory, language-semantic fluency, attention) and Wisconsin Card Sorting Test-perseverative errors ($p = 0.010$) (104). A three-phase exploratory study involving 10 patients with Parkinson's disease receiving recombinant human EPO treatment reported that all the patients showed a favorable and significant increase in the total Dementia Rating Scale score over their baseline status ($p < 0.01$), with the attention subtest also contributing to this change (105). Another study reported that recombinant human EPO administration significantly improved the attention/memory domain score of the Non-Motor Symptoms Scale for Parkinson's disease ($p < 0.01$) and the cognitive domain score of the 39-item Parkinson's Disease Questionnaire ($p < 0.01$) at 12 months in 26 patients with Parkinson's disease (106). In another double-blind, randomized, placebo-controlled, phase II trial on bipolar disorder, EPO was shown to improve processing speed for learning, attention ($p < 0.05$), executive functions ($p < 0.05$), recognition of happy faces ($p < 0.05$), and sustained attention ($p < 0.05$) (107). However, owing to the small sample size or the short duration of these trials, further well-designed trials with a larger sample size and a longer duration are warranted to determine the efficacy of EPO on cognition in these diseases.

SELECTIVE ESTROGEN RECEPTOR MODULATOR

Estrogen receptors are widely distributed over the brain, particularly in the amygdala and the hippocampus that are associated with memory and learning. Some studies investigating the effects of estrogen on postmenopausal women have provided evidence for the efficacy of sex hormones on cognition (108, 109). In our search, we identified four clinical studies that had evaluated the efficacy of raloxifene, a selective estrogen receptor modulator, in patients with schizophrenia. In a double-blind, randomized, placebo-controlled, parallel-design, 12-week study involving postmenopausal women with schizophrenia, significant differences were found in the executive (phonemic fluency task, $p < 0.05$) and memory domains (learning curve, $p < 0.05$) in 16 patients receiving 60-mg daily raloxifene treatment (110). This study demonstrated improvement in some cognitive domains following raloxifene treatment compared to that with placebo in postmenopausal female patients with schizophrenia. However, the sample size of this study is too small to demonstrate generalizability of this result.

Another study identified in our search evaluated the efficacy of raloxifene in patients with Alzheimer's disease. In that randomized, double-blind, placebo-controlled, 12-month pilot study among women with late-onset Alzheimer's disease, it was observed that patients who had received raloxifene (120 mg/day) and placebo showed no significant differences in terms of ADAS-cog change scores at 12 months (111). However, our search yielded no clinical study in the recent decade that had investigated the efficacy of selective estrogen receptor modulators on cognitive enhancement in patients with bipolar disorder and Parkinson's disease. Further clinical studies are required to determine the efficacy of raloxifene on cognitive enhancement in these female patients.

DEHYDROEPIANDROSTERONE (DHEA)

Dehydroepiandrosterone, an important corticosteroid, is a precursor for not only androgenic but also estrogenic steroids. DHEA and its sulfated form (DHEAS) have been reported to modulate the functioning of neurons (112). We found one clinical trial that investigated the efficacy of DHEA on cognition in patients with schizophrenia. It was a 12-week, randomized, double-blind, placebo-controlled study that demonstrated no improvement in cognitive performance (most notably memory) following treatment with DHEA (113). However, in our search, we did not find any clinical study in the recent decade that had evaluated the efficacy of DHEA on cognition in patients with bipolar disorder, Alzheimer's disease, or Parkinson's disease.

CONCLUSION

Schizophrenia, bipolar disorder, Alzheimer's disease, and Parkinson's disease are devastating brain disorders that are associated with lifetime disability and dysfunction in society. Improvement in cognitive function is critical for patients with these disorders. The acetylcholinesterase inhibitors donepezil and rivastigmine might have beneficial effects on cognitive deficits in patients with Parkinson's disease. The effects of memantine on cognition in patients with schizophrenia and Parkinson's disease still remain undetermined. Newer antipsychotics, including paliperidone, lurasidone, aripiprazole, ziprasidone, and BL-1020, have shown possible cognitive benefits than other antipsychotics or placebo in patients with schizophrenia in some clinical trials. Varenicline showed efficacy in terms of cognition improvement in schizophrenic patients, whereas nicotine did not. The α7 nicotinic receptor agonist, such as encenicline, might have cognitive benefits in patients with schizophrenia. Dopamine agonists or agents for enhancing dopamine activity showed little effect on cognitive improvement in patients with bipolar disorder or Parkinson's disease. The NMDAR enhancers, including D-serine, sodium benzoate, and L-carnosine showed cognitive benefits in patients with schizophrenia. NMDAR enhancers might also have cognitive benefits in patients with Alzheimer's disease or Parkinson's disease. EPO demonstrated little evidence of cognitive benefits among patients with schizophrenia, bipolar disorder, or Parkinson's disease. The selective estrogen receptor modulator raloxifene might have cognitive benefits in postmenopausal female patients with schizophrenia. Although few multiyear, prospective, clinical studies evaluating cognitive enhancement following treatment have been conducted, the results of several compounds for the diseases described in this review remain inconsistent. Therefore, additional long-term, well-designed, and large-scale trials are warranted to determine the effects of these medications on cognition improvement in patients with schizophrenia, bipolar disorder, Alzheimer's disease, or Parkinson's disease.

AUTHOR CONTRIBUTIONS

W-YH, H-YL, and C-HL involved in conception, literature review and interpretation, and manuscript writing. All authors reviewed the manuscript.

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Effects of Continuing Oral Risperidone vs. Switching from Risperidone to Risperidone Long-Acting Injection on Cognitive Function in Stable Schizophrenia Patients: A Pilot Study

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Objectives: Risperidone is the first new generation antipsychotic drug to become available as a long-acting injection (LAI). The purpose of this study was to evaluate the effects of switching from oral risperidone to risperidone LAI (RLAI) on cognitive function in stable schizophrenia patients compared with the effects of continuing oral risperidone.

Methods: Sixteen stable patients who had received risperidone monotherapy for at least 3 months were enrolled (the RLAI group). Before and 24 weeks after switching to RLAI, the Japanese-language version of the Brief Assessment of Cognition in Schizophrenia (BACS-J) and the Positive and Negative Syndrome Scale (PANSS) were administered. To exclude the possibility of learning effects on the BACS-J results, 14 patients with stable schizophrenia who continued oral risperidone treatment were also assessed (the RIS group).

Results: The two groups did not differ with respect to changes in the PANSS score, and no emergent side effects, including extrapyramidal symptoms, were observed. The BACS-J score for verbal memory exhibited greater improvement in the RLAI group than in the RIS group ($p = 0.047$).

Conclusion: The results of this preliminary study suggest that switching from oral risperidone to RLAI may improve verbal capability more than continuing with oral risperidone. However, these findings must be replicated in a larger, double-blind study.

Keywords: schizophrenia, risperidone, risperidone long-acting injection, cognitive function, clinical symptoms

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INTRODUCTION

Schizophrenia is a chronic disease with an intermittent course and numerous relapses over time (1). Relapses of schizophrenia are known to adversely affect many biosocial factors (2), and antipsychotic treatment is pivotal for preventing relapse (3). In clinical settings, patients with schizophrenia adherence is often worse and difficult to prevent relapse (4), which greatly impacts the risk of relapse (5).

Abbreviations: BACS, brief assessment of cognition in schizophrenia; JART, Japanese Adult Reading Test; LAI, long-acting injection; RLAI, risperidone long-acting injection; PANSS, Positive and Negative Syndrome Scale.

Risperidone is one of the most widely used atypical antipsychotic drugs for acute schizophrenia treatment. We always continue with maintenance phase treatment after acute phase treatment. However, most patients experience relapse because of low medication adherence, high stress levels, and problems with the use of alcohol and/or drugs. Treatments that are deliverable as long-acting injections (LAIs) are among the more useful therapies in clinical settings.

Recent trends in the treatment of schizophrenia include providing recovery-oriented care, which emphasizes the need to improve cognitive and social functioning such that each patient can achieve his or her treatment goals. Therefore, psychiatrists regard cognitive function as an important treatment target. Recent some meta-analysis shows there were no significant different between LAI antipsychotics and oral antipsychotics regarding efficacy, and safety in schizophrenia (6–9). However, same drug head-to head, but different formulation, studies evaluating the cognitive function of antipsychotics in schizophrenia are lacking.

In this study, we evaluated the effects of switching from oral risperidone to risperidone LAI (RLAI) on cognitive function in stable schizophrenia patients compared with the effects of continuing oral risperidone.

MATERIALS AND METHODS

Sixteen patients with schizophrenia who had received risperidone monotherapy for at least 3 months were included in this study (the RLAI group). All patients had been receiving oral or liquid risperidone treatment for at least 3 months. Patients with a concomitant medical state were eligible to participate in the study if their condition had been stable for at least 3 months and they had been receiving standard therapy for the concomitant condition(s) for at least 1 month. Patients were excluded if they had an untreated or unstable clinically significant medical condition, any clinically significant abnormalities upon laboratory examination or physical examination or if they had a thyroid function abnormality. Other reasons for exclusion included a history of seizures, recent drug or alcohol abuse, a principal psychiatric condition other than schizophrenia, and a suicide attempt during the current psychotic episode. To exclude the possibility of learning effects on the cognitive function, 14 patients with stable schizophrenia who took oral risperidone were also evaluated as continuing group (the RIS group).

Japanese-Language Version of the Brief Assessment of Cognition in Schizophrenia (BACS-J)

Trained psychiatrists assessed cognitive function using the BACS-J (10). The BACS-J, which has well-established reliability and validity, is designed to measure cognitive function in individuals with schizophrenia. Results were adjusted for the influence of age by utilizing age-matched cohorts of controls to calculate BACS-J *z*-scores for each patient with schizophrenia in the present study.

Procedure

Patients in the RIS group continued their treatment with the same dose of risperidone. This dose had been determined based on each patient's clinical status, with an upper limit of 12 mg/day. Patients in the RLAI group received an initial 25-mg injection with overlap with oral risperidone for at least 3 weeks. The maintenance target dose for RLAI was 25 mg every 2 weeks, with an allowable dose range of 25–50 mg every 2 weeks based on the clinician's judgment. After the crossover period, oral supplementation was permitted for acute exacerbations of positive symptoms, but long-term use (>4 weeks) of an ongoing combination of oral antipsychotic and RLAI was not permitted. Injections were given at a treatment room onsite and were typically administered by a nurse practitioner.

Assessments were completed before and 24 weeks after the initial injection by independent raters. Symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS), and cognitive function was assessed using the BACS-J. Daily dose of risperidone were converted to approximate chlorpromazine equivalents (CPZeq) using published article (11). Written informed consent was obtained from all of the participants of this study. The Ethics Committee of the University of Occupational and Environmental Health approved the study protocols, which included standard procedures for clinical research involving vulnerable participants in Japan.

Statistical Analysis

Only data from patients who completed all 24 weeks of the study were evaluated. The raw data collected at baseline and at the study end point were used for statistical analysis. To ensure group comparability, baseline clinical characteristics were tested using *t*-tests or Pearson's chi-square test, as appropriate. Repeated-measures analysis of covariance was performed for each cognitive and social variable, with the baseline data serving as the covariate. For the primary analyses, the between-subjects factor was the group (the RLAI and RIS groups), and the within-subjects factor was time (before and 24 weeks after the initial injection). The effects of group, time, and group-by-time (the interaction effect) were examined. All statistical tests were two-tailed, and a *p*-value less than 0.05 was regarded as indicative of significance.

RESULTS

Demographic and Clinical Characteristics

Thirty patients were allocated into the two groups at the start of the study. No patients dropped out of the study. Therefore, the final analyses included the 30 patients who completed the study. Demographic data for these patients are shown in **Table 1**. At baseline, the two groups did not differ significantly with respect to age, onset, sex, total PANSS score, total antipsychotic dose (in CPZeq) or education.

Clinical Symptoms and Dosage of Risperidone

Changes in the PANSS score from baseline to the study endpoint did not differ between the two groups (**Table 2**).

At baseline, the RLAI and RIS group did not differ with respect to dose of risperidone. Paired *t*-tests demonstrated that after 24 weeks, dose of the risperidone was significantly decreased in the RLAI group.

Cognitive Function

At baseline, the RIS and RLAI groups did not differ with respect to any of the BACS *z*-scores. Paired *t*-tests demonstrated that after 24 weeks of treatment, the *z*-scores for verbal memory, motor function, verbal fluency, attention and processing speed and executive function were significantly improved in the RLAI group, and the *z*-scores for working memory, motor function, verbal fluency, and executive function were significantly improved in the RIS group.

In an analysis of changes in BACS *z*-score from baseline to the study endpoint, the verbal memory *z*-score showed greater improvement in the RLAI group than in the RIS group ($p = 0.047$). There were no significant between-group differences in changes in other scores, including the total score for each scale (**Table 2**).

DISCUSSION

The most clinically relevant finding obtained in this preliminary study is that patients who switch from oral risperidone to RLAI might demonstrate greater improvement in verbal memory than patients who continue oral risperidone treatment. Although the observed between-group differences in the effects on cognitive function were extremely small, our results might have implications for the treatment of schizophrenia. However, the precise mechanism underlying these results remains unknown. In this study, dose of the risperidone was significantly decreased in the RLAI group. Recently report indicate that negative association was found between verbal memory function and dose of risperidone in schizophrenia (12). Moreover, another study reported that dose reduction of risperidone dosage improve the cognitive function in schizophrenia (13). We speculate that these dose reduction might contribute to significant improvement in RLAI group. Furthermore, our findings may be explained by more stable concentrations of risperidone LAI than of oral risperidone or some oral RIS group participants were low adherence than RLAI group.

In the present study, there were no differences between the two groups with respect to changes in the total PANSS score. This result suggests that continuing oral risperidone and switching from oral risperidone to RLAI exhibit similar efficacy.

This study has several limitations. First, the small sample size increased the risk of false-negative findings. A lack of multiple testing correction may also have resulted in type I errors; however, given the pilot nature of the present study, the results obtained in this investigation should be regarded as preliminary. Therefore, replicate studies are needed, possibly with larger samples and a randomized, double-blind design. Second, this study's open-label design might have impacted the results, since the expectations of patients or raters might have affected the assessments. Third, we did not consider blood levels of risperidone at the times of cognitive assessments or other assessments. These blood levels may have affected the outcomes of evaluations (14), although drug level fluctuations are considerably smaller for LAIs than for orally administered antipsychotics (15).

In conclusion, this pilot study suggests that relative to continuing oral risperidone treatment, switching from oral risperidone to RLAI may produce greater improvements in verbal memory.

TABLE 1 | Demographic and clinical characteristics of the participants at baseline.

	RLAI group	RIS group	*p*-Value
Sex (M/F)	7/9	7/7	n.s.
Age (years)	31.5 ± 5.3	27.8 ± 7.6	n.s.
Education (years)	12.9 ± 2.7	13.6 ± 2.5	n.s.
Smoking	12/4	10/4	n.s.
Onset	24.3 ± 4.6	21.9 ± 3.3	n.s.
PANSS-P	16.5 ± 3.6	17.4 ± 4.5	n.s.
PANSS-N	18.7 ± 2.0	18.1 ± 2.9	n.s.
PANSS-G	32.4 + 6.3	36.0 + 4.8	n.s.
PANSS-T	67.8 ± 7.8	71.4 + 8.6	n.s.
DIEPSS	0.3 ± 0.9	1.2 ± 1.8	n.s.

PANSS, Positive and Negative Syndrome Scale; P, positive scale score; N, negative scale score; G, general psychopathology subscale score; T, total score; DIEPSS, drug-induced extrapyramidal symptoms scale.

TABLE 2 | Cognitive function changes in the RLAI and RIS groups.

	RLAI group			RIS group			Time–group interaction	
	0 W	26 W	*p*-Value	0 W	26 W	*p*-Value	*F*	*p*-Value
Chlorpromazine-equivalent of risperidone dosage (mg/day)[a]	278.1 ± 122.3	234.6 ± 64.0	0.015	275.0 ± 152.9	285.7 ± 135.1	0.53	2.58	0.11
PANSS score	67.8 ± 7.8	66.7 ± 7.3	0.049	71.4 ± 8.6	70.3 ± 7.3	0.15	0	0.68
Verbal memory	−1.24 ± 0.91	−0.68 ± 0.72	<0.01	−1.12 ± 1.11	−1.10 ± 0.61	0.92	3.91	0.047
Working memory	−0.98 ± 0.73	−0.84 ± 0.64	0.21	−1.02 ± 0.69	−0.93 ± 0.77	0.49	0.13	0.72
Motor function	−0.82 ± 0.96	−0.69 ± 0.85	0.048	−0.96 ± 0.98	−0.70 ± 0.75	<0.01	0.42	0.52
Verbal fluency	−1.02 ± 0.73	−0.83 ± 0.54	0.048	−1.01 ± 1.32	−0.72 ± 0.88	<0.01	0.56	0.46
Attention and processing speed	−1.60 ± 1.30	−1.21 ± 0.93	<0.01	−1.51 ± 1.13	−1.34 ± 1.00	0.09	1.40	0.25
Executive function	−1.41 ± 2.00	−0.97 ± 1.19	0.02	−1.38 ± 1.96	−0.89 ± 0.95	0.01	0.02	0.89
Composite score	−1.18 ± 0.62	−0.87 ± 0.36	<0.01	−1.17 ± 0.45	−0.95 ± 0.32	<0.01	0.88	0.36

[a]*"Time × group" interaction effect on analysis of variance with BACS-J when compared with the RLAI group.*

However, this finding must be replicated in a larger, double-blind, randomized controlled trial.

ETHICS STATEMENT

Written informed consent was obtained from all of the participants of this study. The Ethics Committee of the University of Occupational and Environmental Health approved the study protocols, which included standard procedures for clinical research involving vulnerable participants in Japan.

AUTHOR CONTRIBUTIONS

HH designed the study, performed the cognitive battery, collected the clinical data, performed the statistical analyses, wrote the first draft of the manuscript, and managed the literature searches. RY developed the study protocol and wrote the final manuscript. AK and KA collected the clinical data. All of the authors took part in either drafting the article it critically for important intellectual content, and approved the final manuscript.

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REVIEW
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Potential and Challenges for the Clinical Use of D-Serine As a Cognitive Enhancer

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After 25 years of its discovery in the rat brain, D-serine is a recognized modulator of synaptic plasticity and cognitive processes through its actions on the NMDA-glutamate receptor. Importantly, cognitive impairment is a core feature of conditions, such as schizophrenia, Alzheimer's disease, depression, and aging, and is associated to disturbances in NMDA-glutamate receptors. The D-serine pathway has been associated with cognitive deficits and these conditions, and, for this reason, D-serine signaling is subject of intense research to probe its role in aiding diagnosis and therapy. Nevertheless, this has not resulted in new therapies being incorporated into clinical practice. Therefore, in this review we will address many questions that need to be solved by future studies, regarding D-serine pharmacokinetics, possible side effects, other strategies to modulate its levels, and combination with other therapies to increase its efficacy.

Keywords: cognitive enhancer, biomarker, sodium benzoate, D-amino acid oxidase, glycine

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INTRODUCTION

In a landmark study, Hashimoto and colleagues (1) discovered the presence of a substantial amount of D-serine in the rodent brain. In the following year, they reported that D-serine is present in high concentration in the human brain as well (2). Interestingly, it was later shown that D-serine is enriched in brain regions that contain a high concentration of the *N*-methyl-D-aspartate receptor (NMDAR), such as the cerebral cortex, hippocampus, amygdala, and retina (3).

The source of D-amino acids in mammals used to be attributed to diet or intestinal bacteria (4), until Wolosker et al. (5) identified serine racemase (SR) as the endogenous source of D-serine through racemization of L-serine. SR was first described to be exclusively present in astrocytes (5–8), but subsequent work has shown that SR is also present in neurons. Kartvelishvily et al. (9) demonstrated robust SR staining in neurons of the rat forebrain, and synthesis of D-serine by primary neuronal cultures. Additionally, a study using *in situ* hybridization confirmed that SR mRNA is predominantly expressed in rat brain neurons (10). Confirming a predominant neuronal expression, another group found the presence of SR in glutamatergic and GABAergic neurons of the mouse forebrain, but not in astrocytes (11).

In a more recent study, Benneyworth and colleagues (12) observed a 60% reduction in SR expression when SR was knocked out specifically in glutamatergic neurons. On the other hand, the knockout in the astrocytes caused a ~10% decrease in SR expression, while the remaining SR

Abbreviations: AD, Alzheimer's disease; CSF, cerebrospinal fluid; DAAO, D-amino acid oxidase; GlyT1, glycine uptake transporter 1; MDD, major depressive disorder; LTP, long-term potentiation; NMDAR, *N*-methyl-D-aspartate receptor; SR, serine racemase.

(~30%) was ascribed to other types of neurons. Importantly, *in vivo* work with microdialysis showed that neurons release D-serine (13). Finally, D-serine and SR are localized to neurons but not astrocytes in mouse and human brains (14). D-serine degradation is achieved through D-amino acid oxidase (DAAO), a flavin-dependent oxidase, resulting in the production of hydrogen peroxide, hydroxypyruvate, and ammonia (15). DAAO is especially enriched in the hindbrain, but it can also be found in the cortex and hippocampus, and it is present in glial cells and neurons (15).

The overlap between D-serine and NMDAR localization in the brain spurred investigations into a possible functional relationship between them. The NMDAR act as a coincidence-detector, as it requires not only binding of agonists but also depolarization of the postsynaptic membrane, which suspends the receptor blockade by Mg^{2+}. The NMDAR is a tetrameric ion channel that may be composed by many configurations of three subunits, GluN1, GluN2, and less commonly, GluN3 (16). To be activated, the NMDAR requires simultaneous binding of the agonist glutamate to the GluN2 subunit and co-agonist glycine to GluN1. This binding is crucial for NMDAR activation, but later findings showed that D-serine is more potent both at binding to the co-agonist site and stimulating the receptor (17). Moreover, depletion of D-serine diminishes NMDAR activity (18) and long-term potentiation (LTP), a form of synaptic plasticity associated to learning and memory (19), and the relevance of D-serine to synaptic plasticity has been demonstrated in different brain regions (7, 20, 21).

Given the contribution of D-serine to LTP, and the fact that LTP is considered a key mechanism underlying learning and memory (22), it was no surprise when studies confirmed the importance of D-serine to learning and memory processes. For example, genetic inactivation of SR (23) and an acute stress protocol that diminishes D-serine levels (24) results in cognitive deficits. Importantly, the finding that the glycine modulatory site was not saturated *in vivo* (25) prompted investigations on whether exogenous D-serine administration could act as a cognitive enhancer. Remarkably, D-serine given intraperitoneally to rats increases NMDAR activation in the hippocampus (26), improves social memory in rats (27) and recognition and working memory in mice (28). Several animal studies now have confirmed the potential of D-serine as a cognitive enhancer, as well as its therapeutic potential in preclinical models. Here, we will review the evidence for the usefulness of D-serine cognitive-enhancing properties in different brain disorders and in age-related cognitive decline, including potential side effects and strategies to increase its efficacy.

SCHIZOPHRENIA

Schizophrenia is a severe neuropsychiatric disorder characterized by positive symptoms (hallucinations and delusions) and negative symptoms (apathy and avolition). Less known is the fact that most patients with schizophrenia also present cognitive impairments (29). Importantly, the degree of cognitive impairment is the best predictor of the daily functioning of a patient (30–32). Interestingly, many neurotransmitter systems important for cognition were found to be altered in schizophrenia, such as the dopaminergic, glutamatergic, cholinergic, and serotoninergic. These neurotransmitter systems are the target of most of the compounds evaluated for cognitive enhancement in schizophrenia, though none has been approved for clinical use.

Accumulating evidence indicates that the glutamate NMDAR might be hypoactive in schizophrenia. Pioneering studies with healthy human volunteers showed that infusion of different types of NMDAR antagonists induces a schizophrenia-like phenotype (33, 34). In addition, the NMDAR antagonist phencyclidine causes positive symptoms and deteriorates cognition in medication-free patients with schizophrenia (35). Interestingly, Steiner et al. (36) found a higher prevalence of NMDAR antibodies in the serum of acutely ill patients with schizophrenia, and polymorphisms in NMDAR subunits have been associated with the disorder (37). Finally, a recent study showed reduced protein levels of NMDAR subunits in *postmortem* samples of the dorsolateral prefrontal cortex in schizophrenia (38).

As discussed before, D-serine is the most potent endogenous co-agonist of the NMDAR. Remarkably, genetic mice models that present diminished D-serine levels recapitulate many aspects of schizophrenia, including sensorimotor gating and memory deficits (23, 39), reduced expression of BDNF (40), and brain ventricular enlargement (41). Notably, lower D-serine levels were found in blood, cerebrospinal fluid (CSF), and *postmortem* brain tissue of patients with schizophrenia (42–45). The decrease in D-serine levels in schizophrenia has been associated to increased levels of G72, a putative activator of DAAO (46–49). Accordingly, increased activity of DAAO has been found in postmortem samples of the cerebral cortex and the cerebellum in patients with schizophrenia (50, 51). Although negative findings have also been reported (52), a recent meta-analysis concluded that D-serine levels are reduced in the blood of patients with schizophrenia (53).

Considering that D-serine may be diminished in schizophrenia and its role in many brain processes affected in the disorder, several studies evaluated its efficacy as an add-on therapy to antipsychotic medication. Although generally safe, there are concerns about potential nephrotoxicity with D-serine (see Side Effects). Despite that, doses tested so far seem to converge to 30 and 60 mg/kg for historical reasons, as the first D-serine placebo-controlled trial for schizophrenia observed improvements in positive, negative, and cognitive symptoms with 30 mg/kg (54). However, while this dose has produced inconsistent results, 60 mg/kg or higher doses repeatedly resulted in therapeutic improvement, be it in chronic (55, 56) or prodromal patients (57). In fact, a recent meta-analysis showed that D-serine improved the positive and negative symptoms when added to antipsychotic drugs (53).

Another potential strategy to increase D-serine availability in the brain is reducing its degradation by DAAO. However, since DAAO is predominantly expressed in the midbrain, medulla, pons, and cerebellum and has relative low affinity for its substrates, some authors argue against a physiological role of DAAO in controlling D-serine availability in areas of the brain relevant for cognition and symptoms of schizophrenia (58). Yet several lines of evidence indicate that DAAO plays a role in controlling

D-serine availability in the forebrain. Systemic administration of a DAAO inhibitor increased levels of D-serine in the rat cerebral cortex (59) and two different studies found increased levels of D-serine in the cerebral cortex and hippocampus of DAAO knockout mice (60, 61), although others studies did not replicate these findings (62, 63). Further evidence on a physiological role for DAAO in modulating cognition is provided by enhanced learning abilities of DAAO knockout mice (64, 65). Finally, in one clinical trial, the DAAO inhibitor sodium benzoate improved several symptoms and cognition in patients with chronic schizophrenia (66).

Other studies focused on glycine, the other endogenous NMDAR co-agonist. Initial studies with small samples found that very high doses of glycine (250 mg/kg or higher) reduced behavioral symptom severity in patients with schizophrenia (67, 68). Clinical use of glycine requires high doses because it does not readily cross the blood–brain barrier, which stimulated the study of drugs that could enhance extracellular glycine levels by inhibiting its reuptake. Accordingly, early studies with a small sample found that chronic treatment with sarcosine, an inhibitor of the glycine uptake transporter 1 (GlyT1), led to generalized improvements in symptoms of patients with schizophrenia (69, 70). Bitopertin is the first specific GlyT1 inhibitor, which showed potential in a Phase II trial (71), but a subsequent trial showed no significant improvements in primary outcomes (72). When interpreting the lack of effectiveness of the inhibition of GlyT in schizophrenia, it is important to highlight that electrophysiological data indicated that glycine, as opposed to D-serine, acts primarily at extra-synaptic NMDAR receptors, which are not required for LTP, and this might reduce the procognitive effect of enhancing glycine levels (73). We, therefore, believe that enhancement of D-serine levels poses a more suitable approach for development of new treatments for schizophrenia. In fact, a recent study compared the effect of chronic D-serine or bitopertin on mismatch negativity—an event-related potential to an odd stimulus in a sequence of similar stimuli—and on clinical symptoms. D-serine led to improvements on mismatch negativity, which correlated with changes in clinical symptoms. Bitopertin, on the other hand, did not change any of those measures (74).

An important question at this point is whether the improvements seen so far with the addition of D-serine will have real-life effects. This has not been generally investigated, but it would be a crucial finding to make the case for the use of D-serine in clinical practice. In contrast, increasing D-serine levels through DAAO inhibition with sodium benzoate was shown to improve quality of life and Clinical Global Impression (66). Interestingly, a recent study found that a combination of sodium benzoate and the GlyT1 inhibitor sarcosine improves cognition and global functioning of patients with schizophrenia, whereas sarcosine alone had no effect (75). However, because of the lack of a group of patients receiving sodium benzoate alone, we do not know whether there was a synergistic effect between the two compounds or the effects came from sodium benzoate only.

It is also important to consider which factors may or may not pair well with D-serine. For instance, there is evidence that D-serine is not effective when combined with clozapine compared to other antipsychotics (76), possibly because the mechanism of action of clozapine might include an increase in D-serine release (77). Indeed, clozapine treatment in patients with schizophrenia can increase plasma D-serine levels relative to L-serine (78). Conversely, it is reasonable to hypothesize that D-serine may lead to better outcomes when used in the subgroup of patients that have evidence of decreased D-serine signaling, a personalized approach not used so far.

D-Serine may also be useful in enhancing the effectiveness of other strategies to improve cognition in schizophrenia, such as cognitive or vocational training. To our knowledge, this has been tried only once, but the authors did not find any advantage of using D-serine along with 40 h of computerized cognitive training, as compared to training only (79). However, it is noteworthy that placebo produced pronounced effects, which may have obscured treatment-specific improvements, and the dose of 30 mg/kg D-serine used in the study has been previously shown to be ineffective to improve cognition in schizophrenia (55). Finally, the pharmacokinetics might play an important role, as D-serine has a short half-life of about 4 h (24, 55), and one can expect important fluctuations on blood levels after a single dose per day. Perhaps, it would be more advantageous to have an increase in D-serine concomitantly with the cognitive training. Animal studies could investigate this question specifically and provide valuable insight on how to increase D-serine effectiveness. An analogous approach has been tried with D-cycloserine, a partial NMDAR agonist. One study found that combined administration of D-cycloserine (once in a week) and a cognitive training (auditory discrimination training) led to better performance in the practiced training but failed to transfer its benefits to other untrained cognitive tasks (80). As the authors discuss, D-cycloserine has the disadvantage of being prone to cause tolerance, which may hinder its therapeutic effect in chronic treatments. However, this study is important because it shows that enhanced performance during training is not sufficient to enhance transfer of benefit to untrained cognitive tasks.

Furthermore, it is important to bear in mind that patients with schizophrenia generally live in an environment lacking sufficient cognitive stimulation, as they are typically unemployed and not pursuing education, partly because of untreated cognitive deficits. Merely stimulating the D-serine pathway to enhance neuroplasticity may be not enough to change maladaptive neural circuits formed throughout a patient's life. For this reason, we believe that in the case of schizophrenia, therapies aimed at increasing D-serine signaling might prove more useful when combined with therapies that expose patients to learning experiences, such as cognitive training, which may induce the formation of more adaptive neural circuits.

AGE-RELATED COGNITIVE DECLINE

There has been a dramatic increase in the life expectancy of the world population in the last decades. Consequently, the rise of number of older adults is a global phenomenon that is becoming a challenge for public health. Aging is an important risk factor for many diseases, but even otherwise "healthy" older adults may present age-related cognitive decline (81). Aging is associated

with declines in a number of cognitive domains, such as processing speed (82), memory (83), learning (84), working memory (85), executive function (86, 87). Importantly, declines have been found also in the primary processing of sensory input, such as visual processing (88), Gestalt detection (89), and speech processing (90). It is possible that declines in lower order processing of information (bottom-up) might contribute to declines in higher order processes (top-down), as degraded inputs may hamper the functioning of higher order circuits.

The age-related cognitive decline becomes important in older adults since it is associated with poorer quality of life, less independence (91), and higher incidence of falls (92, 93). Mobility is a crucial aspect of quality of life in older adults, and the cognitive decline can hamper the ability to drive, affecting social activities and independence, further contributing to depressive symptoms (94). As walking in our fast-paced and complex world requires attention, it is no surprise that cognitive deficits in older adults are associated to gait stability and falls (95). The association between cognition and different aspects of life makes it imperative to understand the underpinnings of the age-related cognitive decline and to develop new strategies for prevention.

In an effort to find molecular underpinnings associated to the age-related cognitive decline, studies in rodents revealed that aging is associated with reductions on the magnitude of LTP in the hippocampus, possibly because of alterations of NMDAR signaling (96). Several studies have revealed an age-related decline in the activation of NMDAR associated with a decrease in D-serine levels in the hippocampus (97, 98), possibly due to a decrease in SR expression (99). It is noteworthy that older LOU/C/Jall rats, which are resistant to age-related memory deficits (100), do not present a decrease in D-serine levels or SR expression with age (99). Finally, our group observed a negative association between plasma D-serine levels and age in healthy subjects (45). Putting together, these studies indicate that an age-related decrease in D-serine could contribute to the progression of the cognitive decline.

These findings raise the appealing possibility that increasing NMDAR activity might be of therapeutic value for the age-related cognitive decline. Accordingly, D-serine administration has been shown to improve cognition in older rodents and to correct many, though not all, of age-related declines in synaptic plasticity (101). From a clinical perspective, it is important to highlight that in a recent double-blind placebo-controlled cross-over study our group observed that an acute oral administration of 30 mg/kg of D-serine improved spatial learning and problem solving, but not working memory, visual attention or cognitive flexibility, in older adults (102). Future studies should investigate whether higher doses of D-serine have a higher efficacy, and, crucially, whether a chronic treatment is tolerable and results in real-life effects, such as improved quality of life and reduced number of falls.

ALZHEIMER'S DISEASE (AD)

Alzheimer's disease is a chronic and progressive neurodegenerative disease that affects more than 6% of adults over 65 years of age worldwide (103), with an estimated global economic cost of $818 billion in 2015 (104). The pathophysiology involves synaptotoxicity, accumulation of extracellular β-amyloid (Aβ) aggregates and intracellular neurofibrils, gliosis, loss of neurons, and brain atrophy (105). Synaptic loss is critically involved in AD pathophysiology, and evidence indicates a possible causal role for glutamatergic dysfunction.

Activation of NMDAR may have different effects depending on the cellular location of the receptor. While LTP depends on activation of synaptic NMDAR, excessive activation of the extra-synaptic or synaptic NMDAR leads to high intracellular Ca^{2+} levels, which may cause cell death, a phenomenon termed excitotoxicity (73). For this reason, tight regulation of extracellular levels of glutamate is crucial. Astrocytes uptake glutamate from the extracellular space through different types of sodium-dependent excitatory amino acid transporters, and then glutamate is converted into glutamine by glutamine synthetase, transported back into the glutamatergic neuron, where it is hydrolyzed into glutamate by phosphate-activated glutaminase (106).

Evidence indicates that excessive NMDAR activation may contribute to AD pathology. Our group and others have shown that different forms of Aβ aggregates increase glutamate release from neurons and astrocytes, which leads to synaptic loss *via* inhibition of synaptic NMDAR currents and stimulation of extra-synaptic NMDAR currents (107–109). As reviewed in Rudy et al. (110), there are a plethora of studies linking AD pathology and an excess of glutamatergic activity, and, in line with this, memantine is a noncompetitive NMDAR antagonist approved for the clinical treatment of moderate to advanced AD.

As a result, dysfunctional D-serine metabolism could be associated to the increased NMDAR activity in AD and perhaps be a target for drug development. In fact, one study found that $SR^{-/-}$ mice, which showed marked decrease in D-serine levels, are protected from injection of Aβ peptide, suggesting that D-serine could be a downstream element of Aβ toxicity (111). On top of that, it was shown that Aβ aggregates induce D-serine release, and D-serine levels are increased in animal models of AD (107, 112, 113). It could be the case that excess D-serine contributes to neuronal death in AD through excitotoxicity.

The question whether D-serine levels are altered in the brain in AD has been controversial. Studies in postmortem tissue found unaltered D-serine levels in different brain regions in AD, including the frontal, temporal, and parietal cortices (114–116). On the other hand, three different studies observed an increase in D-serine levels in the CSF of patients with AD, but the size of the differences between AD and controls varied greatly between studies (113, 117, 118).

It is tempting to speculate that the D-serine increase observed in the CSF of AD patients might be part of a protective mechanism to counter Aβ signaling and prevent AD pathology. Importantly, D-serine has been shown to increase neurogenesis and survival of newborn neurons (119) and to regulate apoptosis in a biphasic way, being able to inhibit it during its early-phases or stimulate it on later phases (120). This implies that increasing D-serine levels in the early-phases of AD might be therapeutically useful [while the NMDAR antagonist memantine is not effective in this

early-phase of AD (121)]. The litmus test, then, is a clinical trial with patients with AD. Strikingly, a randomized, double-blind, placebo-controlled trial showed that 6 weeks of daily treatment with the DAAO inhibitor sodium benzoate improved cognitive composite and Clinician Interview Based Impression of Change plus Caregiver Input scores in patients in early-phase of AD (114). On the other hand, the clinical benefit of DAAO inhibition in AD may be mediated by an antioxidant effect, since D-serine degradation by DAAO generates hydrogen peroxide, one of the reactive oxygen species. Interestingly, there is evidence of increased DAAO levels in the peripheral blood of patients with mild cognitive impairment or AD, and the peripheral DAAO levels are positively associated with the severity of cognitive impairment (115). Moreover, in an animal model of AD, sodium benzoate attenuated oxidative stress and protected memory and learning (116). It is important to note, though, that the therapeutic effect of sodium benzoate might arise not only from its antioxidant effects but also from its immunomodulatory effects (122). In any case, if those clinical findings are replicated, sodium benzoate might prove to be a breakthrough for the treatment of patients in early-phases of AD.

DEPRESSION AND ANXIETY

Major depressive disorder (MDD) is a multidimensional disorder characterized by at least one discrete depressive episode lasting at least 2 weeks and involving, among others, sleep disturbances, anhedonia, anxiety, feelings of worthlessness, and diminished ability to think and concentrate. In the US, MDD has a lifetime morbid risk of 29% (123), and its estimated annual cost is higher than US$ 80 billion (124). Notably, MDD is the second leading contributor to global disease burden, expressed in disability-adjusted years (125). Although cognitive impairment is a formal criterion item of a major depressive episode, its contribution to psychological suffering and functional outcome has been largely underappreciated. It is significant that the cognitive impairment persists after the resolution of an acute episode (126), and it is a predictor of functional outcome (127).

Animal models spurred the idea of an involvement of the NMDAR in the etiology of MDD, which gained momentum after the discovery that a single sub-anesthetic dose of ketamine elicits rapid and long-term antidepressant effects (128). Accordingly, preclinical and clinical work supports the idea of an overactivation of NMDAR in MDD (129), and different NMDAR antagonists show promise as potential antidepressants (130). However, a recent meta-analysis concluded that in adults with MDD ketamine has limited efficacy after 1 week of treatment, and the effects were even less pronounced after 2 weeks (131). Evidence was limited by risk for bias and the small number of participants and there were very limited data on issues like safety, tolerability, efficacy for cognition, quality of life, and costs to health-care services.

It is surprising that, in the same meta-analysis, the only other glutamate receptor modulators to show some efficacy in MDD was sarcosine, a glycine transporter inhibitor, that works by enhancing NMDAR activity (the opposite of ketamine) (131). Not only sarcosine, but also D-serine has shown antidepressant properties in both mice and humans (130, 132). In mice, acute D-serine administration has antidepressant and anxiolytic effect similar to ketamine (133), and chronic high levels of D-serine (through exogenous administration or overexpression of SR) reduced the proneness toward depression-related behavior (134). Accordingly, an acute single dose of D-serine improved mood in healthy human adults (135) and showed antidepressant-like effect in rats mediated by activation of AMPA-glutamate receptors and increased brain-derived neurotrophic factor, similar to that of ketamine (136). In addition, D-serine chronic administration can increase adult neurogenesis and survival of newborn neurons in mice (119) and regulate the functional synaptic integration of adult-born neurons (137), both processes that are associated to the therapeutic effect of antidepressants (138).

Consequently, despite our current incomplete understanding of the role of the NMDAR in MDD, data from rodents and humans warrants further research on the effect of D-serine administration in MDD patients. D-serine has a relatively safe profile, and its usefulness might be twofold, as it could improve both mood and cognition of the patients, hopefully giving them a better quality of life.

Interestingly, animal work has revealed that D-cycloserine can facilitate the extinction of fear memory, possibly because of the role of the NMDAR in synaptic plasticity and learning and memory (139). Building on this, many studies investigated whether D-cycloserine could facilitate the effectiveness of exposure-based therapy, which involves exposing the person to the feared context but in the absence of danger, so that relearning may occur (140). This effect was confirmed by a meta-analysis that showed that D-cycloserine can contribute to exposure-based therapy by increasing its efficiency, but the effects decrease over repeated sessions (141). More recently, D-cycloserine was shown to potentiate the effects of cognitive behavioral therapy in patients with anxiety disorders (142). Although results with D-cycloserine to promote the efficiency of behavior therapy are promising, this is a partial co-agonist of NMDAR with effects that diminish with the time. On the other hand, little is known about the effects of full co-agonists of NMDAR, such as D-serine or analogous agents, on the efficacy of behavior therapies in anxiety and depressive disorders.

SIDE EFFECTS

Although the majority of people do not experience side effects with D-serine, there is a concern that D-serine might induce nephrotoxicity in humans, as is the case with rats (143). Evidence indicates that nephrotoxicity is due to D-serine metabolism by DAAO, as rats that lack the enzyme do not develop glycosuria nor polyuria after high doses of D-serine (144). Therefore, co-administration of a DAAO inhibitor with D-serine may be a strategy to not only increase oral bioavailability of D-serine but also to prevent nephrotoxicity (145). This synergism has been observed mice, as treatment with a DAAO inhibitor rendered a small dose of D-serine (30 mg/kg) effective to treat prepulse inhibition deficits caused by the NMDAR antagonist dizocilpine, as opposed to the same dose of D-serine alone (146). It is conceivable that a combination of D-serine and sodium benzoate in future

clinical trials will allow the use of lower doses of both drugs while retaining a high efficacy.

Alternatively, because D-serine and sodium benzoate have different pharmacokinetic and pharmacodynamic profiles, it is possible that each one of them might prove more effective and/or safe for different conditions. For instance, D-serine may be especially useful for depression because of its acute and chronic antidepressant effects, whereas sodium benzoate may be a safer approach in older adults with impaired renal function. In schizophrenia, a meta-analysis found that D-serine improves symptoms with small effect-sizes ($d < 0.4$), while one study found that higher doses of D-serine (60 mg/kg or higher) improve cognition with large effect-sizes ($d > 1.0$) (55). In contrast, in one study that warrants replication, twice daily administration of sodium benzoate (1 g/kg) improved cognition, symptoms and global functioning with large effect-sizes (all > 1.0) (66). Perhaps sodium benzoate had a higher efficacy because it not only inhibits DAAO but also modulates the immune system and has antioxidant properties, both of which may play a role in schizophrenia (147, 148). Future studies are needed to confirm the effectiveness of benzoate and its best doses for the treatment of schizophrenia.

CONCLUSION AND PERSPECTIVES

Pharmacological modulation of the D-serine pathway presents promising therapeutic opportunities for treatment of a variety of conditions that have in common cognitive and emotional disturbances. Specifically, D-serine and sodium benzoate are cheap and relatively safe drugs that have been administered to people taking a variety of other drugs. We believe future studies must aim to identify predictors of response across different conditions, in order to maximize the therapeutic effect of these drugs.

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GG and RP designed, wrote, and reviewed the manuscript.

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REVIEW
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Drugs Interfering with Muscarinic Acetylcholine Receptors and Their Effects on Place Navigation

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Muscarinic acetylcholine receptors (mAChRs) have been found to regulate many diverse functions, ranging from motivation and feeding to spatial navigation, an important and widely studied type of cognitive behavior. Systemic administration of non-selective antagonists of mAChRs, such as scopolamine or atropine, have been found to have adverse effects on a vast majority of place navigation tasks. However, many of these results may be potentially confounded by disruptions of functions other than spatial learning and memory. Although studies with selective antimuscarinics point to mutually opposite effects of M1 and M2 receptors, their particular contribution to spatial cognition is still poorly understood, partly due to a lack of truly selective agents. Furthermore, constitutive knock-outs do not always support results from selective antagonists. For modeling impaired spatial cognition, the scopolamine-induced amnesia model still maintains some limited validity, but there is an apparent need for more targeted approaches such as local intracerebral administration of antagonists, as well as novel techniques such as optogenetics focused on cholinergic neurons and chemogenetics aimed at cells expressing metabotropic mAChRs.

Keywords: scopolamine, biperiden, acetylcholine, receptor, behavior, learning, memory, rodents

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INTRODUCTION

Acetylcholine (ACh) is one of the major neurotransmitters and modulators of the nervous system. Its receptors are abundantly expressed in a wide variety of tissues, from neuromuscular junctions and parasympathetic system to cortical regions involved in cognitive functions such as learning and memory (1). The cholinergic system has been shown to play an important role in processes such as circadian rhythmicity (2), addiction (3), motivation, pain, and reward (1), as well as cognitive flexibility (4), perceptual memory (5), spatial learning (6), and many more. It comes as no surprise that abnormalities in the function of the cholinergic system and its components underlie a multitude of pathologies, such as Parkinson's disease (7), Alzheimer's disease (AD) (8), schizophrenia, bipolar disorder (9, 10), and depression (11). For these reasons, the cholinergic system has been extensively studied in recent years; however, many mechanisms of its function still remain unclear.

Abbreviations: ACh, acetylcholine; AChE, acetylcholine esterase; AChR, acetylcholine receptors; AD, Alzheimer's disease; Asn, asparagine; CNS, central nervous system; DMP, delayed matching to position; GPCRs, G-protein-coupled receptors; mAChR, muscarinic acetylcholine receptors; MDMA, 3,4-methylendioxy-metamphtamine; MWM, Morris water maze; nAChR, nicotinic acetylcholine receptors; QNB, quinuclidinyl benzilate.

ACh SYSTEM IN THE BRAIN

There are two main types of ACh receptors, named historically after their naturally occurring alkaloid agonists: (1) nicotinic receptors (nAChRs), a family of ionotropic receptors which act as ligand-gated cation channels and (2) muscarinic Ach receptors (mAChRs), a metabotropic G-protein-coupled receptor (GPCRs) family whose activation may trigger various responses depending on the specific subtype and context of the signal (8). Nicotinic ACh receptors are named after nicotine, their prototypical agonist. Probably the most famous antagonist of the nAChRs is D-tubocurarine, a compound isolated from the curare poisons (12, 13). mAChRs are named after muscarine, a toxic alkaloid synthesized in the toadstool *Amanita muscaria*. Possibly the best known antagonist of the mAChRs is atropine, found in the deadly nightshade (*Atropa belladonna*) (14).

Nicotinic Receptors

Despite being best known for their involvement in signal transduction at neuromuscular junctions, these receptors are also expressed throughout the central nervous system (CNS). As mentioned above, nicotinic ACh receptors are ionotropic, i.e., ligand-gated cation channels, whose activation by an agonist evokes a flux of K^+, Ca^{2+}, and Na^+ ions (however not all subtypes of nAChRs are permeable for Na^+), which in turn triggers mechanisms of Ca^{2+} signaling (1). These receptors typically comprise five subunits: either a homomeric combination of α subunits (for example α7) or a heteromeric combination of α(1–10), β(1–4), δ, and ε subunits. The specific combination of these subunits results in different pharmacological properties of the individual subtypes, such as ion selectivity and ligand affinity (14). The most common nAChR subtypes found in the brain are α7 and α4β2 receptors. Located at both pre- and postsynaptic sites, they play a pivotal role in various processes, such as learning and cognition (15), decision-making (9), and regulation of the postnatal development of the visual cortex (16). Thus, nicotinic ACh receptors constituted of specific subunits appear to be suitable pharmacological target for cognitive enhancement.

Muscarinic Receptors

Muscarinic receptors are abundantly expressed throughout the brain; however, they are also found in various other tissues in the body, such as the heart (17, 18), the bladder and pulmonary system (19), and the intestine (20). As mentioned above, mAChRs do not serve as cation channels like nicotinic receptors, but instead are coupled with G-proteins, which transmit signals into the cell by affecting the activity of certain enzymes (such as the adenylyl cyclase, phospholipase C, etc.) (14, 21).

Five subtypes of mAChRs have been described, M1–M5. They differ in their level of expression in various parts of the body and the signal cascades they trigger after binding an agonist. Located mostly postsynaptically, the M1, M3, and M5 receptors (sometimes referred to as "M1-like" receptors) activate phospholipase C *via* $G_{q/11}$ protein, thus inducing a calcium influx into the cell. M2 and M4 on the other hand (the "M2-like" group), when activated lower the level of cyclic adenosine mono-phosphate in the cell by $G_{o/i}$ protein-mediated inhibition of adenylyl cyclase. They are found both pre- and postsynaptically (8, 21, 22).

The outputs of signaling through specific cholinergic receptor subtypes may vary tremendously depending on the subtype of the receptors and their pre- or postsynaptic localization. The specific tissue and the type of the cell that expresses the receptors is also of major importance, as well as the metabolic state of the neuron at the precise time of receiving the signal, i.e., a cell with high intracellular levels of calcium may react differently to a signal than one with low intracellular concentrations of calcium. To further complicate any predictions of outcomes of cholinergic signaling and behavioral analysis, many neurons corelease ACh and glutamate, or ACh and gamma-aminobutyric acid (4, 21).

One of the major characteristics of the molecular structure of mAChRs is the evolutionarily highly conserved orthosteric ACh binding site, with a key asparagine residue (Asn105). This results in great difficulty when developing direct agonists and antagonists selective for a specific receptor subtype, and non-selective agents such as scopolamine, an antiemetic drug, and 3-iodothyronamine are widely used in research on memory impairment (23–25). Researchers have rather focused on developing compounds acting as allosteric ant/agonists and positive allosteric modulators (8, 26).

M1 mAChR

The M1 receptor is considered to be the most abundant subtype (50–60% of all mAChRs) of mAChRs in the brain. It plays an essential role in many cognitive functions such as learning and memory, and thus has become a target of research focusing on developing therapeutics for neurodegenerative diseases (8, 10, 27). For example, Ragozzino et al. (28) reported an enhancing effect of CDD-0102A, a partial M1 agonist, on working memory and strategy changing in rats. The compound improved the rats' performance in a spontaneous alteration task (designed to test working memory) and, under changed circumstances, their ability to deem a previously useful strategy irrelevant and to find and retain a new one. They demonstrated the involvement of M1 receptors in these processes, and further suggested the use of CDD-0102A as a potential therapeutic agent for disorders such as AD and schizophrenia, emphasizing its enhancing influence and the lack of observed adverse effects (28). The M1 receptor is also expressed in other tissues than the brain; for example it has been shown to participate in the regulation of non-quantal ACh release in neuromuscular junctions (29).

ANTIMUSCARINIC DRUGS

Due to the diverse expression and functions of AChR in the brain, compounds affecting the cholinergic neurotransmission are employed in the treatment of a wide range of conditions and diseases. They are generally used for antiparkinsonian treatments, specifically targeting extrapyramidal symptoms such as rigidity, tremors, and bradykinesia. For example, it is generally accepted that an imbalance of cholinergic and dopaminergic transmission in the brain is one of the mechanisms underlying or accompanying schizophrenia, particularly in the negative

symptoms and cognitive impairment. Anticholinergic drugs are often prescribed along with antipsychotics to alleviate their unwanted side effects. However, their usage has often been questioned as they themselves cause a range of side-effects, such as cognitive impairment, tardive dyskinesia, blurred vision, dry mouth, problems with urinary retention, psychosis, addiction, and many more (30–32). To give an example, Veselinović et al. (33) investigated the effect of the administration of anticholinergics on cognition in untreated patients with schizophrenia and healthy control subjects. Their results showed a marked impairment in both groups, which was however more pronounced in the schizophrenia patients, thus again casting doubt on the suitability of these drugs in the treatment of schizophrenia (33).

Interestingly, some antimuscarinic agents (namely scopolamine) also appear to possess antidepressant qualities, especially in treatment of those patients who are unresponsive to the standard therapy. Witkin et al. (11) reported that these antidepressant effects might be mediated specifically by the blockage of the M1 and M2 receptors (11).

The general consensus is that anticholinergics disrupt acquisition learning and long-term memory processing. As such, these compounds are often employed for inducing memory and cognitive impairments in laboratory animals in order to model pathological states observed in human diseases such as schizophrenia, AD and other dementias (5). Despite its popularity, such an approach has received a lot of criticism. For example, antimuscarinic agents provide only a limited predictive and face axes of validity, but low construct validity in AD research. Furthermore, it is sometimes very difficult to tease apart effects on memory and attention, or procedural deficits in general, that are separable from the cognitive deficits in many navigational tasks (34).

Mechanisms of Action

As mentioned above, the ACh binding site is evolutionarily highly conserved across all five mAChR subtypes, which in turn complicates the search for subtype-selective ligands. However, there is an abundance of allosteric sites that facilitate receptor activity modulation and are specific for each receptor subtype. These have enabled the development of highly selective compounds (8).

Orthosteric subtype-selective agents are scarce, though some may be found; for example, a recent study reported a novel compound PCS1055 that exhibits high selectivity for the M4 receptor (35). Also, some ligands have been shown to bind at the orthosteric site as well as one of the allosteric sites, thus achieving relatively high selectivity for a specific mAChR subtype. An example may be seen in the work of Jakubík et al. (36), where the mechanism of action of the M2-selective antagonist methoctramine was put under scrutiny. The authors reported that methoctramine binds with high affinity to the orthosteric site and at the same time interacts with lower affinity with an allosteric site at the second and third extracellular loops. Interestingly, in the presence of another orthosteric-binding ligand (such as N-methyl-scopolamine), methoctramine may still bind to the allosteric site, thus preventing the other ligand from dissociating from the receptor. This antagonist occasionally binds the M3 receptor as well, but with a much lower affinity due to the lack of the allosteric site found on M2 (36). Also, the time that antagonists take to bind to the receptor has been shown to be of crucial importance for the efficacy of receptor blockage. For example, due to its relatively slow binding, tiotropium seems less effective at blocking the M3AChR (37).

As to the effects of antimuscarinic drugs on the organism, these naturally depend on the means and site of administration (which determines where the agent exerts its influence, such as the brain following an intracerebroventricular injection or the heart after a systemic application of a drug unable to cross the blood–brain barrier). Thus, as the M1 and M4 receptors are abundantly expressed in parts of the brain affected in neurodegenerative diseases such as AD, it seems probable—and has been repeatedly reported—that stimulating cholinergic transmission *via* these receptors should enhance cognitive abilities, learning and memory, whereas blocking it would result in cognitive impairment (26).

Clinical Potential of Antimuscarinic Drugs

In spite of the risk of various undesirable side-effects such as cognitive impairment, dry mouth, or even psychosis and addiction, if dosed with care, antimuscarinic drugs provide therapeutic effects in a number of conditions. For illustration, aclidinium and tiotropium are often prescribed in the treatment of chronic pulmonary disease, as well as asthma, overactive bladder, and irritable bowel syndrome (38–41).

Quite recently, scopolamine, a non-selective antagonist capable of crossing the blood–brain barrier, has been found to exhibit antidepressant properties (mediated probably by its binding to M1 and M2 receptors), even in patients unresponsive to standard therapy (11). This has proven beneficial not only to patients with major depressive disorder but also to those suffering from bipolar disorder (42). In addition, scopolamine is also used as an antiemetic, for example in treating postoperational nausea (23).

As mentioned previously, mAChR antagonists (e.g., biperiden, trihexyphenidyl) are also employed as prophylaxis and/or for the treatment of side-effects of antipsychotics prescribed in diseases such as schizophrenia. However, this method is currently on the decline due to the multitude of unwanted side-effects of the anticholinergic treatment (30, 33).

Biperiden, amongst other antimuscarinics, also acts as an antiparkinsonian agent and is thus sometimes prescribed to patients with Parkinson's disease, as well as other diseases manifesting with parkinsonian symptoms. However, even here the risks of addiction and detrimental side-effects still remain (43, 44).

Quite surprisingly, given the amount of criticism regarding the cognitive side-effects of muscarinic antagonists, a recent study investigating the properties of a new potential treatment for AD reported M1-antagonism for these agents. The tested drug candidate was developed using a newly proposed approach to treating multifactorial diseases such as AD, which aims to hit multiple therapeutic targets with a single drug comprising a series of compounds, in this case combining 7-methoxytacrine and memantine. As the results of other tests (such as successful prevention of β-amyloid fibrillization, AChE inhibition, etc.)

looked rather promising, the authors recommended the novel compound as a potential treatment, claiming that the observed M1-antagonism did not seem to exhibit noticeable effects (45). It is conceivable that muscarinic antagonism can act beneficially when it is a part of a broader spectrum of mechanisms of action.

Biperiden As a Prototype Drug

Biperiden hydrochloride (or lactate) is an established M1-receptor selective antagonist. Approved for human usage and sold under the brand name of Akineton, it is prescribed for Parkinsonism (to improve motor abilities such as gait and tremor) and occasionally to suppress the side-effects of neuroleptics.

Apart from clinical practice, biperiden is also used in research as a cognitive impairer (46, 47). Biperiden has been shown to cross the blood–brain barrier without difficulties, thus enabling a simple administration of the drug, such as using intraperitoneal or subcutaneous injections (s.c.). The tissue distribution (V_d) for biperiden has been reported to be relatively high: with a brain to plasma ratio of up to 7–12 (44). The uptake of the drug by the tissues is quite rapid, possibly also due to its substantial transport into lysosomes (48). This makes biperiden a useful candidate as a specific drug, contrarily to scopolamine or atropine.

PLACE NAVIGATION

To increase their chances of survival, including successful foraging for food and other resources, as well as finding their nest or burrow, animals employ a variety of spatial navigation strategies. In principle, such strategies can be based on idiothesis or allothesis (or a combination of both). In the first case, an individual finds its way based on the information from vestibular receptors, muscle proprioceptors and tendon receptors complemented with efference copies of motor commands and/or optic and haptic flow, whereas in the second case, the spatial representation is established upon external cues (49). Three navigation strategies may be used to reach a goal:

(1) *a praxis strategy*, when an animal follows a set of learned, usually stereotypic movements that lead to a known goal,
(2) *a taxon strategy*, when the goal is clearly visible from a distance or marked by other cues,
(3) *a spatial strategy or mapping*, when long-distance external cues become the spatial reference points, as the goal cannot be located otherwise (by sight or smell) (50–52).

To illustrate, a man waking up at night and finding his way to the bathroom in the dark employs a *praxis* strategy; he knows it takes approximately four steps to the door of the room and then he has to turn right in the hallway and walk five more steps. A *taxon* strategy is used for example by a man approaching a bank—a large conspicuous building bearing an easy-to-see "Bank" sign. Finally, the mapping strategy focuses on finding the correct configuration of distal external cues, such as a man searching for a buried treasure (after his unsuccessful trip to the bank): e.g., he has to stand at a place with the big pine tree to his left, the strangely shaped mountain on the horizon behind him, and the lake a short distance in front of him.

Spatial navigation is based on the so-called *place coding* (53). The key structure of the brain involved in these processes is generally thought to be the hippocampus (more specifically its dorsal part); however, other parts of the brain play important roles as well. The neuronal substrate consists of place cells, large hippocampal pyramidal neurons with characteristic complex spikes that fire only in a specific part (or parts) of a given environment [the so-called *firing fields* or *place fields* (54); for review see Ref. (55)]. Interestingly, their structural organization in the brain is not topological, i.e., it does not reflect the outside world. Groups of these cells constitute *ensembles*, which serve as representations of the environment (56). Apart from these, there are grid cells, located in the entorhinal cortex (57). The spatial pattern of their firing fields resembles a hexagonal grid. And the final type is represented by head direction cells, found in the Papez circuit, and whose activity is dependent on the inclination or direction of an individual's head (49, 53, 58–60). The specific roles and mechanisms of function of these cells are not yet fully understood. A recent study has proposed a model for spatial navigation based on cooperation between place cells and grid cells, in which place cells are responsible mainly for locating a goal, whereas grid cells are in charge of directing an individual toward that goal (60).

Other important aspects of effective spatial navigation are sets of spatial stimuli that yield so-called frames of reference. An individual often needs to distinguish and correctly assess conflicting information from several of these frames to solve a task. An example of a behavioral test specifically assessing this ability is active place avoidance (see Active Place Avoidance Tasks). The hippocampus has been shown to be the structure responsible for organizing this spatial information into representations correctly corresponding to the outside world (61–64). Behavioral tests based on spatial navigation are largely used by researchers in studying certain types of memory.

ANTIMUSCARINIC AGENTS IN SPATIAL TASKS

Morris Water Maze (MWM)

Non-Specific Antagonists

Scopolamine is possibly one of the most frequently used antimuscarinic agents in the MWM. In spite of becoming something of a "gold standard" in research of cognitive impairment, its validity as a model has often been questioned because of its considerable side effects. As it lacks selectivity for any of the subtypes of mAChRs, apart from memory and cognition it also affects the sensorimotor functions of the treated subjects, thus sometimes compromising the results of the behavioral tests (65). However, Robinson et al. (66) reported impaired performance in the MWM in both rats and mice following scopolamine administration at a dose that exhibited no effect on visual acuity. This was studied in a variant of the MWM task specially adjusted to test for compromised visual perception, in which the animals were required to discriminate between two marginally differing

cards in order to successfully find the hidden platform (66). A lack of effect on performance in a mainly vision-reliant task (the visible platform variant of the MWM) was also reported by Entlerova et al. (67) in their study focusing on a comparison of two commonly used rat strains (Wistar and Long-Evans) and their performance and sensitivity to anticholinergic blockade in the MWM and active place avoidance. Following scopolamine treatment, they found no marked differences in the MWM between the two strains, whereas in active place avoidance the Wistar rats exhibited significantly worse performance than the Long-Evans group, suggesting a higher sensitivity to scopolamine in the Wistar strain (67).

Furthermore, von Linstow Roloff et al. (68) set out to investigate whether the poor performance of scopolamine-treated rats in the MWM is in any part due to an effect on memory processes, or whether it is just the result of compromised sensorimotor abilities. In a series of experiments consisting of acquisition tasks combined with both spatial and non-spatial pretraining, as well as delayed-match-to-position (DMP) and a variant of the DMP with an on-demand platform [also called the Atlantis platform (69, 70)], they were able to show that although scopolamine undoubtedly causes side-effects leading to altered swimming speeds and higher levels of thigmotaxis, these can be eliminated by extensive spatial pretraining. In such a case however, scopolamine-treated animals still perform more poorly than controls, thus confirming that scopolamine does indeed affect spatial memory. In the Atlantis platform paradigm, the researchers were able to discriminate between the effects on procedural and spatial memory: scopolamine was found to impair the latter (68).

Navigating to a submerged platform requires a mapping strategy. As reviewed in Ref. (6), scopolamine disrupts forming a memory for platform location that is held constant across days (reference memory) or changes daily (working memory). When directly compared, working memory seems to be affected more than reference memory (71). Compromised navigation in the water maze can be explained in terms of the inaccurate positional information of place cells. Intraventricular or intrahippocampal infusions of scopolamine increase the firing of place cells outside of the usual place cell firing field of the neuron, leading to lesser place specificity (72, 73). Scopolamine seems to also affect other correlates of spatial memory. Its systemic administration flattens the typically robust positive correlation between running speed and theta frequency (74) and reduces spatial tuning of the grid cells (75). However, at least in the entorhinal cortex, scopolamine does not alter the tuning of head direction cells (75).

Water maze studies are able to provide some evidence regarding how scopolamine specifically affects particular stages of memory processing. There is general agreement on its effects on memory encoding [reviewed in Ref. (76)], while reports on consolidation or recall are mixed. Most studies report no or little effect on consolidation or recall (6, 77, 78) but a recent investigation demonstrated that systemic scopolamine administration in mice had a detrimental effect on the retrieval of platform location (79).

Scopolamine-induced cognitive impairment has also been shown to possess good validity as a translational model in research. Laczó et al. (80) compared the effects of scopolamine administration (as well as its coadministration with donepezil, an AChE inhibitor) in rats and humans in the MWM and the Hidden Goal Task, an analog of the water maze fit for use in humans. The authors reported successful validation of the tasks and scopolamine, as no significant differences were found between the human volunteers and the animals. Donepezil was shown to exhibit some ameliorative effect; however, this was not clear in all cases (80).

Although mostly of an older date, studies examining the effects of other antimuscarinic agents may also be found. In one such report by Sutherland et al. (52) focused on atropine, atropine sulfate-treated rats were found to lack the ability to employ spatial mapping as means of learning the location of the hidden platform, thus turning to a combination of taxon and praxis strategies (i.e., not remembering the position of the platform but instead rather a way of finding it). No such deficit was observed in control animals and a group treated with atropine methylnitrate (a substance acting solely in the periphery as it is unable to cross the blood–brain barrier), hence confirming the hypothesis that the central cholinergic system underlies spatial mapping strategies (52). It has also been proposed that atropine may interfere with the ability to inhibit non-efficient spatial strategies that appear initially during water maze acquisition (81).

The use of the MWM also occurred in a report assessing the properties of 3-quinuclidinyl benzilate (QNB), a non-selective muscarinic antagonist that has been proposed as a potential agent for modeling cognitive deficits in rats. The study showed a significant detrimental effect of QNB on acquisition in the MWM, whereas no impairment was found in memory consolidation and retrieval. Apart from hyperlocomotion leading to higher swimming speeds, the authors observed no adverse side effects of QNB on vision and sensorimotor functions (82). A study on oxybutynin, an antagonist of M1, M2, and M3 receptors, further confirmed that non-selective antagonists exert detrimental effects on acquisition in the MWM (83).

M1-Like Family mAChR Antagonists

Due to their abundance, it has been suggested that the effects of non-selective antagonists may be exerted primarily through M1 receptors. However, it turned out that attempts to silence M1 receptors functioning have provided mixed results. Pirenzepine, a selective M1 antagonist, was evaluated in the studies of Hagan et al. (84) and Hunter and Roberts (85). Although less potent than scopolamine, it was nevertheless shown to impair spatial navigation in the MWM while preserving the taxon strategy (navigation to a visible platform). However, one of the major drawbacks of this drug is its inability to cross the blood–brain barrier, thus requiring intraventricular administration (84, 85). In contrast to that line of evidence, mice lacking M1 receptors display unimpaired performance in a water maze in spite of general hyperactivity (86). Furthermore, systemic administration of imidafecin, a selective M1 and M3 antagonist, appeared to have no significant effect on navigation in a water maze (83). These results therefore questioned the exclusive role of M1 receptors in scopolamine-induced deficits in water maze navigation. In an attempt to explain this discrepancy, Bubser et al.

concluded that M1 receptors seem to play a more significant role in mPFC-mediated tasks than in hippocampus-dependent tasks (87).

M2-Like Family Antagonists

An exception to the "rule" of muscarinic antagonists having detrimental effects on learning and memory are compounds selective for receptors expressed presynaptically (such as M2), which by blocking the presynaptically mediated inhibition of ACh release actually help to increase the levels of ACh in the synapse, and thus also cholinergic transmission (88, 89). For example, BIBN-99, a selective M2 antagonist, has been shown to improve the performance of aged rats in the MWM (88). Involvement of the M4 receptor in a water maze was assessed using M4 receptor knock-out mice. Despite elevated locomotion observed in the open field, knock-out mice displayed both unaltered acquisition and preference to a target location in probe trials in the water maze (90). It can be generally concluded that M2-like family muscarinic antagonists have weaker and sometimes even positive effects on place navigation tasks due to the different neuronal localization of respective receptors and the *de facto* different mechanistic mode of action, resulting in specific behavioral outcomes.

Results obtained with the MWM generally support the conclusion that antimuscarinic drugs adversely affect place navigation. On the other hand, this task also points to a number of non-cognitive confounding variables in the effects of antimuscarinic agents in place learning and memory. Importantly, muscarinic antagonists specific for particular receptor subtypes have been found to have only partial advantages over non-specific ligands, stressing the need for highly targeted approaches into the physiology of mAChR system with selective opto- and chemogenetic methods.

Radial Arm Maze

The Radial arm maze presents another task used to test spatial cognition, namely working and reference memory, but the procedure may also be adjusted to assess acquisition and memory retrieval (91, 92). This task was used for example in the study of Kay et al. (93), which showed that scopolamine elicits a stronger effect on working memory, while 3,4-methylendioxymetamphtamine administration affects reference memory more prominently (93). Similar results regarding scopolamine administration had also been reported by Pilcher et al. (91), who compared the effects of scopolamine on working memory, acquisition and memory retrieval, concluding that there was stronger impairment in working memory relative to the other types (91).

This task may also be used for investigating differences in the consequences of acute vs. chronic drug administration, as shown for example by Ortega-Alvaro et al. (94). In their study, the authors found a significant impairment in rats' performance in the radial arm maze following an acute injection of atypical antipsychotics (olanzapine and clozapine, used in the treatment of schizophrenia) and scopolamine, marked among others by a lower speed of movement. However, when following a chronic drug treatment, the observed deficits were absent, hence hinting at the ability to build a tolerance. The authors also concluded that chronic muscarinic antagonism may exert little or no influence over working memory (94).

One possible drawback of this task was raised in a study of Hodges et al. (95). The authors pointed out that the peripheral effects of scopolamine administration include "dry mouth," which can lead to disruption of a rat's ability to eat multiple food pellets and thus decrease their reward value.

Spatial Alternation Tasks

The natural tendency of rodents to alternate between two choices in successive trials is exploited in a variety of simple T-shaped or Y-shaped mazes. Due to the simplicity of the task, alternation has been employed in the bulk of pharmacological studies using the scopolamine-induced amnesia model. Numerous studies [reviewed in Ref. (96)] have consistently shown that scopolamine treatment disrupts working memory both in discrete (97) and continuous versions of the alternation paradigm (98, 99). A article by Givens and Olton (100) demonstrated that intraseptal injections of scopolamine mimicked the detrimental dose-dependent effect of systemic scopolamine injections, indicating a critical contribution of the medial septal area. Further studies supported the central position of the septohippocampal pathway and revealed a more distributed network including a few other limbic and non-limbic structures (101).

Intraventricular administration of the M1 antagonist pirenzepine exerts similar effects as scopolamine, suggesting that M1 receptors may dominate in mediating spontaneous spatial alternation (102). On the other hand, M2 knockout mice were found to perform worse only under longer (20 s) but not short (5 s) delays in reinforced alternation in a T-maze compared to wild-type controls (103), suggesting a more complex contribution of particular mAChR types. M5 receptors seem to play a role in alternation as well, but the mechanism of action is likely indirect. As M5 receptors are expressed by endothelial cells and control cerebral vasodilatation, M5R−/− mice were found to exhibit a significantly reduced cerebral blood flow in the cerebral cortex, hippocampus, basal ganglia, and thalamus. In consequence, the low blood supply led to impaired long-term potentiation and consequently to a deterioration of spatial alternation (104).

Despite being almost ubiquitous in pharmacological research, the spatial alternation paradigm has some drawbacks. Investigators do not usually configure the maze to enforce animals to use praxis, taxon, or mapping strategies, or any combination of these. Therefore authors cannot report, in contrast to the MWM, whether effects are due to impairment of a particular mode of place navigation. Furthermore, the variability and consistency of results have been disputed, particularly in the spontaneous alternation paradigm. However, this drawback can be counterbalanced by the fact that under some circumstances, spatial alternation has been found to be superb at detecting hippocampal dysfunction (105).

Active Place Avoidance Tasks

Active place avoidance [(106–117), for review see Ref. (110, 111)] is a behavioral test specifically focusing on a rat's ability to

coordinate two conflicting frames of reference. An animal is placed into a slowly rotating arena where it needs to learn to locate a "to-be-avoided sector," upon which stepping into it receives a foot-shock. The position of this sector does not change relative to the room frame; i.e., the animal has to actively move to another place in the arena so as not to be carried into the sector. The arena's surroundings ought to contain distinct extramaze cues for the rats to navigate (110, 112–116).

The first study with scopolamine in this task (117) showed that a deficit induced by scopolamine at doses 1 and 2 mg/kg was not alleviated by intact spatial pretraining. A follow-up study (67) compared the performance of two rat strains obtained from the breeding colony of Institute of Physiology, CAS, Prague (Long-Evans and Wistar) in the MWM and active place avoidance following scopolamine treatment. As already mentioned, whereas in the MWM the disruption in learning and memory was similar, in active place avoidance the Wistar rats exhibited a higher sensitivity to scopolamine than the Long-Evans group (67). In general, active place avoidance tasks are sensitive to antimuscarinic action elicited by scopolamine, yet the effects are strain-specific and also present at relatively higher doses that can also affect procedural aspects. Unfortunately, no active place avoidance results on more selective antagonists, mAChR knockouts or other specific manipulations with the mAChR system are available, indicating the need for future research.

Barnes Maze

In the Barnes maze, a rat is placed in the center of a circular platform with holes at the edges. An escape cylinder is placed under one of these holes; the animals are trained to locate the position of this cylinder based on distal external cues. The use of odor trails is eliminated by rotating the platform in between trials, and animals presumably use a mapping strategy to locate the target (118).

Evaluations of antimuscarinic agents employing this paradigm are scarce. Consistent with other cognitive mapping taxing tasks, scopolamine was found to impair performance (119). Seeger et al. (103) used this task for investigating changes in cognition and behavior in M2 knock-out mice, reporting a severe impairment in learning, accompanied with decreased short-term and long-term potentiation (103). Another example of the usage of this test is the study by Gawel et al. (120), in which the authors examined the potential of cholinesterase inhibitors (donepezil and rivastigmine) to alleviate ethanol-induced cognitive impairment. The results showed an improvement in both memory retention and cognitive flexibility, the latter being more pronounced for rivastigmine (120).

Cone-Field Test

The cone-field task represents another experimental paradigm for testing spatial learning and memory. It consists of a dodecagonal field with a number of cones topped with un/baited food cups in the middle and four starting boxes on the borders, from which the animal is released into the field. The ability of the rat to learn and remember the position of the baited cones is assessed. A suggested advantage of this test over tasks like the MWM is that it is based on positive reward learning (whereas the MWM relies on aversive learning). This task was used for example by Van der Staay et al. (121) to investigate the effects of AChE inhibitors (donepezil and metrifonate) on scopolamine-induced learning deficits in rats. The results showed that metrifonate, but not donepezil, was able to alleviate the working memory disruption produced by scopolamine (121). Specific conclusions on the role of mAChRs in this task are impossible due to the limited data.

Hole-Board Task

In the hole-board task, an animal is placed in a rectangular box with a number of holes in the floor. Some of these are baited with a food reward. An animal is evaluated in its ability to learn and remember the position (using a mapping strategy) of the baited holes as well as the holes it has already visited. Different variations and adaptions of this task have been used. For example, Post et al. (122) published a article on a hole-board paradigm specially designed for mice (COGITAT) and presented its validation as a tool for testing spatial learning and memory *via* a scopolamine-induced performance deficit and its alleviation by metrifonate (122). Regarding the involvement of particular types of receptors, M1 receptors were shown to be important for reference memory (for non-baited holes) in a study evaluating biperiden in pigs (47). On the other hand, M2 receptors were shown to be important for working memory (memory for already-visited holes) in a study using transgenic mice (123).

GENERAL DISCUSSION AND CONCLUDING REMARKS

The muscarinic system of the brain plays a pivotal role in advanced cognitive processes such as spatial navigation and learning, an extensively studied ability, not only to gain insight into the way humans and animals orient themselves in both familiar and unfamiliar environments, but because spatial memory represents a rodent model of human perceptual memory. Research in this field provides new findings regarding the neurophysiology of higher cognitive processes, as well as pathologies such as those seen in AD and other neurodegenerative diseases, and indicates potential pathways for the therapy and treatment of these conditions.

However, as the muscarinic system is important not only for learning, memory and cognition but also takes parts in other processes such as attention, motivation, sensory perception, and other non-cognitive aspects of behavior, it is no surprise that the blockage of mAChRs also yields a wide range of non-cognitive effects, thus hindering cognition-focused research and complicating interpretations of the effects observed in rodent behavioral experiments. There have been attempts to isolate the purely cognitive effects of muscarinic antagonism from the procedural and motivational aspects, and some have been relatively successful.

One of the more promising ways to study the effects of mAChRs in place navigation lies in the exploitation of local intracerebral administration of antagonists, which ensures no

TABLE 1 | Summary of the overall effects (positive, negative, none) of particular groups of antimuscarinergic agents or transgenic manipulations on spatial performance.

	Non-selectives	M1 group antagonists	M1 knockout	M2 group antagonists	M2 knockout
Water maze	Negative (52, 65, 67, 68, 82, 83)	Negative (84, 85)	None (86)	Positive (88)	
Radial arm maze	Negative (91, 93)				
Alternation	Negative (97–99)	Negative (102)			Negative (103)
Active place avoidance	Negative (67, 117)				
Barnes maze	Negative (119, 120)				Negative (103)
Cone field	Negative (121)				
Hole board	Negative (47, 122)				Negative (123)

M1, M2, muscarinic receptors. Blank cells indicate no data available.

peripheral effects, or the use of specific conditional mutations. Moreover, despite attempts to use more specific muscarininc ligands to eliminate the procedural adverse effect of non-selective antagonists such as scopolamine and atropine, they have often provided ambiguous results. However, Sambeth et al. (24) recently showed that biperiden elicits cognitive deficits extending to the spatial memory domain in humans. It seems that with some caution, a general recommendation of using either non-specific or highly specific antagonists can be provided in conditions with defined place learning strategies having known involvement of the mAChR system.

Nonetheless, the ultimate need and relevance lies in the exploitation of novel techniques such as optogenetics focused on cholinergic neurons, and chemogenetics aimed at cells expressing metabotropic mAChRs. As these methods provide a more precise way to target the mAChR in the CNS, it is conceivable that relatively soon the systemic or even focal application of non-specific antimuscarinic drugs may become a rather obsolete tool for this research. However, the pharmacological development of more specific ligands for mAChRs may yet bring a revival of this traditional neuropharmacology approach. Furthermore, the need for the development of new therapeutics acting on mAChRs will result in an ongoing requirement for testing place navigation as a "prototype" of cognitive functions under the influence of these drugs.

It should also be noted that the choice of a specific behavioral test plays an essential role in the research of cognition, as various tasks examine different aspects of learning and memory (e.g., *praxis* vs. spatial mapping) and may possess higher or lower sensitivity toward the observed phenomenon. Furthermore, not all tasks are hippocampus-dependent, and even among those which are not all employ M1 as a crucial part (**Table 1**). Careful attention should also be paid to the rodent strain used; for example, albino rats such as the Wistar strain have difficulty learning vision-reliant tasks. Well-planned rodent behavioral studies with carefully thought-out experimental designs will continue to provide a useful tool for research on the muscarinic system and its role in learning and memory.

AUTHOR CONTRIBUTIONS

JS, AP, and AS wrote major parts of the manuscript. JS and AS contributed to revisions of the manuscript. AS provided scientific leadership and student supervision. The article is based on the thesis of AP.

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MINI REVIEW
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Dose Reduction/Discontinuation of Antipsychotic Drugs in Psychosis; Effect on Cognition and Functional Outcomes

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Backgrounds: There is a debate regarding the optimal timing of discontinuation of antipsychotic drugs in patients with first episode psychosis (FEP) or schizophrenia. We aimed to provide a review of the literature on which strategy (medication maintenance vs. dose reduction/discontinuation) is more likely to maximize outcomes, such as cognition and social function.

Methods: Using PubMed, the Cochrane Library and systematic reviews, articles published between 2007 and 2018 were reviewed, which investigated the effect of dose reduction/discontinuation vs. maintenance treatment on measures of cognition and/or social function in FEP and schizophrenia.

Results: Six studies were identified; 2 studies reported on cognition while 4 studies concern social function. All studies except one reported that improvement of functional outcomes in remitted patients with FEP or schizophrenia allocated to a dose reduction/discontinuation arm was equal to or better than that in patients for whom medication doses were maintained. One trial of social function with a 1-year follow-up period found a greater improvement in the medication maintenance group, while no group difference was observed with 3-year and 10-year follow-up periods. On the other hand, a 7-year follow-up study found a superiority for the dose reduction/discontinuation regimen in terms of social outcome. Two studies on cognition with a short follow-up period reported a greater improvement for the dose reduction/discontinuation group.

Conclusions: Information on cognition and social function has been relatively sparse. These measures of functional outcome should be considered in deciding which strategy of antipsychotic treatments is beneficial in individual cases with FEP or schizophrenia.

Keywords: first episode psychosis, schizophrenia, discontinuation, maintenance, antipsychotics, cognition, social function, functional outcome

INTRODUCTION

There is controversy about the continued use of antipsychotic drugs in patients with psychotic disorders, including schizophrenia. For example, treatment guidelines for first episode psychosis (FEP) recommend at least 1-year of antipsychotic treatment following remission (1). Antipsychotic medication may affect relapse and remission rates over time. In fact, randomized controlled trials (RCTs) have reported a considerably high relapse rate after dose reduction/discontinuation of antipsychotic treatment (2–5). From the clinical point of view, the maintenance/discontinuation debate should also encompass other aspects, such as functional outcome.

Functional outcome consists of several domains, such as psychosocial skill acquisition, instrument skills/social problem-solving ability, and community outcome/daily activities (6). A general consensus is that recovery in psychosis contains achievements of a personally acceptable quality of life and feeling of self-esteem (7). These outcome measures have been suggested to receive a higher priority than symptom management for young people with psychosis (8). Specifically, there is convincing evidence for an association between cognition and functional recovery in schizophrenia, as cognition may provide a better correlate of functional outcome than psychotic symptoms (6, 9). Accordingly, Sumiyoshi et al. (10) reported temporal associations between cognition and social function in patients with schizophrenia. Longitudinally, Fu et al. (11) found that performance on tests of attention, verbal learning, and verbal working memory are associated with social function throughout a 4-year observation period. Consequently, efforts have been made to develop therapeutics for disturbances of cognition (10).

To date, effects of antipsychotic drugs on cognition in patients with schizophrenia have been intensively examined. Initially, the second-generation antipsychotic drugs (SGAs) were suggested to ameliorate cognitive impairment more effectively than the first-generation antipsychotic drugs (FGAs). However, results from recent meta-analyses of RCTs on the effect of SGAs vs. FGAs, or SGAs vs. placebo indicate that only clozapine elicits cognitive benefits in patients with schizophrenia (12–14). So far, no consensus has been established as to an appropriate duration of antipsychotic treatments, particularly with regard to cognitive and social outcomes.

Some clinicians may feel that the quality of life (QOL) in patients with FEP would be better if antipsychotic medications are discontinued following remission (15). To our knowledge, there has been little information on the effects of maintenance vs. dose reduction/discontinuation of antipsychotic treatments on cognitive and social function in patients with FEP or schizophrenia. Therefore, the aim of this article is to provide an overview on which strategy is more beneficial for these outcomes.

MATERIALS AND METHODS

Search Strategy and Selection Criteria

We searched PubMed, the Cochrane Library, and systematic reviews for randomized and non-randomized controlled trials published between 2007 and 2018, using the following search string; (schizophrenia OR psychosis OR first episode) AND (dose reduction OR discontinuation) AND (cognition OR social OR function OR relapse OR remission OR recovery). We also searched the reference lists of previous reviews, which compared the effects of medication maintenance vs. dose reduction/discontinuation on relapse, remission, cognition, and/or social function in FEP or schizophrenia (16–19). The searches were limited to English language articles and titles/abstracts. Due to the limited number of RCTs on functional outcome between the two groups (dose reduction/discontinuation vs. maintenance) in FEP, we included open-label randomized controlled trials and non-randomized prospective studies.

RESULTS

Study Design

We have identified five open-label and one double-blind studies comparing cognitive and/or social functional consequences between maintenance and dose reduction/discontinuation of antipsychotic treatments in patients with FEP or schizophrenia. Out of them, five were RCTs (3, 4, 20–23), whereas one was a non-randomized, prospective study (24). A summary of these studies, including the methodology and results, is presented in **Table 1** (for comparisons between studies, relapse rates were calculated, where necessary, by diving the number of patients who relapsed during observation periods by the total number of patients in the corresponding group). Subjects included patients with schizophrenia, schizophrenia spectrum disorders, or FEP, with various regimens in terms of medication dose reduction/discontinuation, follow-up period, and outcome measures. Sample sizes ranged from 42 to 178, and the length of follow-up ranged from 28 weeks to 10-years.

Outcome Measures

Two studies included measures of cognition, while 4 studies used measures of social function at follow-up.

Faber et al. (20) used a test battery consisting of the Stroop 2 (color naming) and 3 (color-word naming) tests, continuous performance test (CPT), digit span forward and backward, California Verbal Learning Test, Trail-Making A and B, verbal (category) fluency (animals and professions), Symbol Substitution Test, and Finger tapping (25, 26). These tests have been shown to represent attention, working memory, verbal memory, cognitive speed of processing, and motor speed.

Takeuchi et al. (22) assessed cognition with the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (27, 28). This battery yields scaled scores for 5 cognitive domains, i.e., immediate memory, visuospatial/constructional ability, language, attention, and delayed memory.

Gaebel et al. (4) assessed social function with the Global Assessment of Functioning (GAF) (29). This scale measures symptom severity, as well as psychological, social, and occupational functioning during specified periods, on a continuum from mental health (score 100) to mental illness (score 0) (30). QOL was measured by the Lancashire Quality of Life Profile (LQLP) (31). The LQLP focuses on nine specific

TABLE 1 | Cognition and social function in maintenance vs. dose reduction/discontinuation of antipsychotic drugs in psychosis.

Study and year	No. of subjects	Subject population	Study design	Follow-up period	Outcome measure	Relapse rate (%)	Cognition	Social function
Gaebel et al. (4)	MM 23 /MD 21	Clinically stable first-episode schizophrenia (ICD-10), aged 18–56, with antipsychotic treatment for 12 months and 8 weeks	RCT, OL, during the last 1-year of the 2-years and 8 weeks follow-up, comparison MM with MD (targeted intermittent treatment after stepwise drug discontinuation), risperidone or haloperidol	1-year	GAF	MM 0 < MD 19[a]		GAF score (mean) MM (79.4) > MD (62.1)[a] LQLP (mean) MM 5.3: MD 4.8, NS
Faber et al. (20)	MM 20 /MD 22	FEP, having reached remission within 6 months of the start of second generation antipsychotics	RCT, OL, comparison MM with MD, risperidone, haloperidol or quetiapine	2–3 months	Stroop test, CPT, digit span, CVLT, TMT, verbal fluency, Symbol Substitution, Finger tapping		Improvement on Symbol Substitution, verbal fluency, TMT B MM < MD[a]	
Wunderink et al. (21)	MM 52 /MD 51	FEP in remission for 6 months	RCT, OL, during the last 2-years of the follow-up, comparison MM with MD, doses below 1 mg of haloperidol equivalents	7-years	GSDS	MM 68.6:MD 61.5, NS *Symptomatic remission; MM 66.7: MD 69.2, NS*		% functional remission MM (19.6) < MD (46.2)[a]
Takeuchi et al. (22)	MM 30 /MD 31	Schizophrenia (DSM-IV) in remission with respect to positive symptoms and treated with stable doses of olanzapine or risperidone	RCT, OL, comparison MM with MD (dose reduced by 50%), olanzapine or risperidone	28 weeks	RBANS	MM 3.0: MD 3.0, NS	Improvement in RBANS scale score (mean) MM (−0.1) < MD (+7.0)[a]	
Mayoral-van Son et al. (24)	MM 22 /MD 46	FEP with antipsychotic treatment ≥ 18 months, stabilized at the lowest effective dose ≥ 3 months, clinical remission ≥ 12 months, functional recovery ≥ 6 months	Nonrandomized, prospective study, OL, comparison MM with MD (discontinuation), amisulpride, aripiprazole, haloperidol, olanzapine, quetiapine, risperidone, ziprasidone	3-years	DAS	MM 31.8 < MD 67.4[a]		% functional recovery (DAS global score = 0) MM 90.9: MD 84.8, NS
Chen et al. (3) and Hui et al. (23)	MM 89 /MD 89	First-episode schizophrenia (DSM-IV) with full positive symptom resolution after about 2-years of antipsychotic treatment, aged 18–65	RCT, DB, comparison MM with MD (early discontinuation) for 12 months, quetiapine	10-years	SOFAS, RFS, SF-36	Relapse at 12 months MM 30 < MD 63[a] Composite poor outcome at 10-years MM 21 < MD 39 [a]		SOFAS score (mean) MM 61.9: MD 64.0, NS RFS total score (mean) MM 21.3: MD 21.5, NS SF-36: MCS score (mean) MM 50.2: MD 51.0, NS SF-36: PCS score (mean) MM 56.6: MD 56.9, NS

CPT, continuous performance test; CVLT, California Verbal Learning Test; DAS, Disability Assessment Schedule; DB, double blind; FEP, first episode psychosis; GAF, Global Assessment of Functioning; GSDS, Groningen Social Disability Schedule; LQLP, Lancashire Quality of Life Profile; MD, medication dose reduction/discontinuation; MM, medication maintenance; OL, open label; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; RCT, randomized controlled trial; RFS, the Role Functioning Scale; SF-36, the 36-Item Short Form Health Survey; MCS, mental component summary; PCS, physical component summary; SOFAS, the Social and Occupational Functioning Assessment Scale; TMT, Trail-Making Test.

[a]*Statistically significant; NS, no significant difference.*

domains; living situation, family, social relationships, leisure activities, work/education, finances, personal safety, health, and religion. The questions pertaining to the subjective QOL appraisal allow patients to rate their satisfaction on a seven-point scale (32).

Wunderink et al. (21) evaluated social function with the Groningen Social Disability Schedule (GSDS) (33), a semi-structured investigator-based interview measuring disabilities in social function. Seven items from the GSDS were used; self-care, housekeeping, family relationship, partner relationship, relationship with peers, community integration, and vocational functioning. A patient with functional remission should function adequately in all 7 domains with none or only a minimal disability in all of them (not allowing a score of 2 or 3).

Mayoral-van Son et al. (24) used the global disability item from the Spanish version of the Disability Assessment Schedule (DAS). This item has a score range from 0 (no disability) to 5 (gross disability). They dichotomized functional status into "functional recovery" and "functional deficits." The "functional recovery" status indicates that the patient is currently participating in part-time (paid and fewer than 35 h per week) or full-time work or study with the same or better level of performance as before the psychotic episode, and has no functional disability (score of 0 in the DAS).

Hui et al. (23) assessed social function with the Social and Occupational Functioning Assessment Scale (SOFAS) and the Role Functioning Scale (RFS), as well as health-related QOL with the 36-Item Short Form Health Survey (SF-36). The SOFAS assesses social and occupational functioning, whose scores are not directly influenced by overall severity of the individual's psychological symptoms (34, 35). The scores range from 1 to 100, with lower scores representing impaired functioning. The RFS measures the functioning level in patients with psychiatric disorders, focusing on four domains; working productivity, independent living and self-care, immediate social network relationships, and extended social network relationships (36). Each domain is rated on a 7-point scale, with lower scores representing lower functioning. The SF-36 consists of 36 questions on functional health and well-being (37), as summarized by two indices, i.e., the mental component summary (MCS) and physical component summary (PCS). The MCS includes four domains; vitality (energetic or fatigued), social functioning, role limitations because of emotional problems, and general mental health (psychological distress and well-being), while the PCS consists of four domains; physical functioning, role limitations because of physical health problems, bodily pain, and general health perceptions. SF-36 scores range from 0 to 100, with higher scores indicating better functional health and well-being.

Relapse Rate

In the reviewed studies, relapse rates range from 3.0 to 67.4% in dose reduction/discontinuation groups, and 0–68.6% in medication maintenance groups. Three trials (3, 4, 24) with a follow-up period less than 3-years reported a higher rate of relapse in the dose reduction/discontinuation groups, while a 7-year follow-up study (21) found that relapse rates of the two groups (dose reduction vs. maintenance) were equal. In a 10-year follow-up study (23), the incidence of persistent positive symptoms, requirement for clozapine, or death by suicide occurred in 39% in the discontinuation group and 21% in the maintenance group (risk ratio 1.84, 95% CI 1.15–2.96; $p = 0.01$).

Cognition

Faber et al. (20) found that the medication discontinuation group showed a significantly greater improvement than the maintenance group on scores of the Symbol Substitution Test ($F = 4.49$, $df = 1.40$, $P < 0.05$), verbal fluency task ($F = 6.11$, $df = 1.40$, $p < 0.05$) and Trail-Making Test-B ($F = 5.54$, $df = 1.40$, $p < 0.05$) at 2–3 months after the start of dose reduction/discontinuation. Similarly, Takeuchi et al. (22) reported that the dose reduction group showed a significantly greater improvement in RBANS scores compared with the maintenance group [mean (SD), 7.0 (7.1) vs. −0.1 (8.0), $p < 0.001$].

Social Function

Gaebel et al. (4) reported that the medication maintenance group showed a greater mean GAF score at 1-year follow-up point than that in the dose reduction/discontinuation group [79.4 (10.1) vs. 62.1 (16.7), $p < 0.001$]. On the other hand, no between-group difference was found for QOL [5.3 (1.2) vs. 4.8 (0.9), NS]. By contrast, Wunderink et al. (21) found that the functional remission rate after 7-years was significantly higher for the dose reduction/discontinuation group compared with the maintenance group (19.6 vs. 46.2%, $p < 0.01$). On the other hand, Mayoral-van Son et al. (24) did not find a difference in the functional status at the 3-year follow-up point between the two groups (90.9 vs. 84.8%, NS). Likewise, Hui et al. (23) did not observe a significant difference in the functional status at the 10-year follow-up point between the two groups; [61.9 (9.6) vs. 64.0 (8.9), NS] on SOFAS [21.3 (3.4) vs. 21.5 (2.8), NS] on RFS Total, [50.2 (9.1) vs. 51.0 (8.4), NS] on SF-36 (MCS) and [56.6 (7.6) vs. 56.9 (6.6), NS] on SF-36 (PCS).

DISCUSSION

The present review identified 2 studies reporting on cognition and 4 studies on social function, which compared functional outcomes between medication maintenance vs. dose reduction/discontinuation patients with FEP or schizophrenia. In spite of abundant information on relapse rates, only the limited number of studies have dealt with these outcomes, particularly, cognition. Of note, all studies except one (4) reported the advantage of the dose reduction/discontinuation method over the maintenance strategy in terms of functional outcomes.

In terms of social function, a trial with a 1-year follow-up period (4) found a greater improvement in the maintenance group, while there was no significant group difference 3-years and 10-years after the start of follow-up (23, 24). On the other hand, the study with a 7-year follow-up period (21) observed a superiority for the dose reduction/discontinuation regimen. The difference in study design may account for the discrepant results.

For example, social function was measured by the GAF in the 1-year follow-up study (4). The GAF assesses psychotic symptoms and overall functional ability simultaneously; when symptom severity and level of functioning are discordant, clinicians are directed to use the rating that reflects the lower of the two levels (30, 38). In the 1-year follow-up study (4), the high relapse rate in the dose reduction/discontinuation group may have affected symptom severity, leading to worsening of GAF scores (assumed to represent "function" status). The use of standardized scale to assess real-world social function, independent of symptom severity, would be desired to circumvent this issue. Regarding the study with a 7-year follow-up period (2, 21), both groups were similar in their interventions, because about 80% in the dose reduction/discontinuation group *failed to discontinue* drug treatment (39). In addition, follow-up was generally naturalistic and unblinded, so there could be a difference in unmeasured psychosocial aspects, such as community care and number of visits (39). Furthermore, the differences in diagnostic categories in the 2 groups may be a plausible explanation toward the significantly better recovery and functional remission in the dose reduction/discontinuation group (40). Further study is warranted to determine the effect of length of observation periods on social function in patients who (dis)continue medications.

A greater improvement in cognition for the dose reduction/discontinuation group was reported in two studies (20, 22) with a relatively short follow-up period of less than 3 months. Fu et al. (11) found that performance on tests of attention and verbal working memory predicted social function, as measured by the Global Functioning (Social and Role) (11), in addition to temporal associations between social function vs. attention, verbal working memory, and verbal learning memory at baseline. Also, a longer observation period revealed that a greater cumulative lifetime antipsychotic use led to poorer cognitive performance in later life in patients with schizophrenia, which may be caused by disorganization symptoms (41). Future studies should consider type of cognitive domains and potential effects of key clinical features on cognitive and functional outcomes.

Part of the results from this review suggests that dose reduction/discontinuation of antipsychotic treatments after remission leads to better functional outcome in FEP and schizophrenia. In addition, Wunderink et al. (21) reported that milder negative symptoms, living together, and better social function at baseline are associated with better functional outcomes. Meanwhile, we often experience chronic patients exhibiting severe functional impairment as a result of repeated relapses after discontinuation of antipsychotic drugs. In fact, Mayoral-van Son et al. (24) found that relapsed patients showed more severe symptoms and poorer functional status at the end of follow-up periods. Further, Gaebel et al. (42) found that social function was significantly poorer in patients who relapsed after drug discontinuation compared to those without relapse. These observations indicate a need for the search of predicting factors to identify patients who need continued medications.

Previous studies have attempted to identify patients who will be benefitted or jeopardized by dose reduction/discontinuation of antipsychotic drugs. Accordingly, Wunderink et al. (21) found that a short duration of untreated psychosis was the strongly associated with achievements of symptom remission. Moreover, Alvarez-Jimenez et al. (16) noted that risk factors of relapse after discontinuation or dose reduction include diagnosis of schizophrenia, longer duration of illness, and poor pre-morbid functioning. They also reported that psychosocial interventions for FEP coupled with antipsychotic drugs were effective in preventing relapses (43). Furthermore, the guidelines devised by the International Early Psychosis Association (1) recommend that the minimal dose antipsychotic medication should be continued for preventing relapse and impairment of functions in FEP patients with risks of relapse.

In conclusion, although dose reduction/discontinuation of antipsychotic medication may be associated with higher relapse rates, this strategy may improve cognitive outcomes in some patients with FEP or schizophrenia. In this line, predictors for successful dose reduction/discontinuation deserve further explorations. So far, information on cognition and social function is relatively sparse. These measures of functional outcome should be considered in deciding which strategy of antipsychotic treatments is encouraged in individual cases.

AUTHOR CONTRIBUTIONS

TS planned and initiated this work. YO performed the literature search and drafted the first manuscript. Both authors revised the manuscript and approved the final version.

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OPINION
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Cognitive Remediation for Schizophrenia with Focus on NEAR

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Keywords: cognition, cognitive remediation, schizophrenia, motivation, intervention

Cognitive remediation or CR is increasingly gaining attention in the field of psychiatry. CR is still a relatively new intervention method for persistent and severe psychiatric illness such as schizophrenia. This article purports to provide general overview of CR and refers to NEAR as its specific example, with the hope that the article will be of help to solicit interest of professionals in psychiatry.

Cognitive remediation has been reported to improve cognition such as attention (1) processing speed (2), immediate learning and memory (1), verbal working memory (3), and problem-solving (4).

In symptomatology of schizophrenia, symptoms are traditionally described in the three groups; positive symptoms, negative symptoms, and thought disorders. More recent literature describing the major symptom groups of schizophrenia might mention positive symptoms, negative symptoms, and cognitive dysfunction. Prevalence of cognitive dysfunction in schizophrenia has been discussed (5). It is observed in more than 80% of people with schizophrenia (5). Cognitive dysfunction occurs as early as the first episode of the illness and persists through the late episodes. Its commonality and severity demand targeting intervention. Severity of the dysfunction varies depending on specific domain of cognition, and most common cognitive domains that are known to be seriously impaired include verbal learning, executive functions, vigilance, motor speed, and verbal fluency (5).

Cognitive dysfunction has been associated with social functioning, such as work, education, independent living, and leisure. More specifically, a study has pointed out that cognition such as vigilance, working memory, verbal memory, and executive functions are positively associated with functional outcomes including social function and occupational function (6). Another study showed that cognition such as working memory, attention, perceptual processing, verbal memory, and processing speed accounted for 52% of functional outcome variance including returning to work or school (7).

While cognitive dysfunction may be considered as a primary feature of schizophrenia, some myths may warrant clarification (5). Cognitive dysfunction is not caused by positive symptoms (5). Cognitive dysfunction is not primarily caused by medications, although there are some exceptions. Although cognitive dysfunction is associated with negative symptoms, it is not caused by negative symptoms. Cognitive dysfunction is not a reflection of overall cognitive decline.

Cognitive remediation was designed as a method of intervention to address cognitive dysfunction. CR may be considered as one of the rehabilitation tools for schizophrenia. As a relatively new method of treatment in psychiatry in Japan, CR is sometimes misunderstood as a choice of intervention for dementia, or as a subtype of cognitive-behavioral therapy. CR is unlike other treatment methods in that it targets neurocognition directly.

Cognitive remediation has several approaches and each has different characteristics, such as use of computer (8), inclusion of employment training (9), focus on a particular aspect such as social cognition (10), or emphasis of motivation (8). CR approaches differ from each other by training focus such as drill practice or strategy, by training model such as rehabilitation or compensation, and by perspectives on hierarchical order of cognition task such as bottom-up perspective or top-down perspective.

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When new psychosocial intervention approach such as CR is introduced, its dissemination is often dependent upon practical issues. Effectiveness of CR is tested in a controlled laboratory setting, which is difficult to replicate in a real-world, clinical setting (11). Ease of delivery, clinician training, and clinician supervision, appear to affect which method of CR is selected by a site. Structured or manualized method of CR is generally preferred, as the presence of a structure in a psychosocial intervention tends to improve treatment or implementation fidelity (11).

Delivery of CR has challenges in some settings, such as non-English speaking countries. When CR uses computer software programs, finding appropriate ones may pose difficulty, as the same software programs mentioned in CR treatment manuals may not be available or usable due to language issues. Likewise health insurance system differs depending on a country where CR is delivered, and affects if and how CR may be offered.

NEAR is a form of CR and stands for Neurocognitive and Educational Approach to (Cognitive) Remediation. NEAR was developed by Medalia and her colleagues (12). In NEAR, two computerized sessions and one verbal session a week are typically offered. Sessions are offered in a small group format, which facilitates interpersonal aspect of rehabilitation. NEAR is based on educational principles and emphasizes intrinsic motivation (IM). NEAR has been effective in improving cognition and social functioning (13). The improvement has been maintained as long as 4-month follow-up (13).

NEAR is based on learning principles and views CR as a form of education (14), as CR asks individuals to do something in a new manner. In a traditional learning model, individuals' ability determined the learning outcome, leaving small room for change by intervention. However, in a more recent learning model, individuals' cognitive ability, motivation, and mode of instruction all affect one another, determining learning outcomes (15).

In NEAR, intake interview is conducted prior to a patient's enrollment in a group. Cognition is assessed prior to the beginning of NEAR, and relevant background information is gathered such as educational history, employment history, learning styles, and rehabilitation goals. In some instances, a neuropsychological testing may be conducted to measure cognition. Rehabilitation goals may be in the domains of education, employment, independent living, or leisure, and it is desirable that these goals are specific. Specific rehabilitation goals may be used to illustrate how mastering a specific cognitive task is helpful in real life.

People with severe psychiatric illness such as schizophrenia tend to have impairment in motivation, as noted in avolition or anhedonia. IM has been studied as a mediating factor between cognition and social functioning (16). The need for intervention for schizophrenia to enhance IM has been shown (17). It has been demonstrated that CR that enhances IM, compared to CR which does not, improves the sense of competence, and cognition more significantly (8).

There is a range of motivation from rather external to IM (18). Motivation has been linked to behaviors, and an externally motivated individual may engage in a particular behavior due to external forces or encouragement such as teacher, medical staff, a high test score, or monetary reward. An intrinsically motivated individual may engage in a particular behavior because he/she may regard the behavior as interesting, enjoyable, valuable, or at which they are competent. Intrinsically motivated individuals may engage in a behavior when they consider that they are autonomously choosing the behavior, and it is not forced upon them.

Intrinsic motivation theoretically is based on self-determination theory or SDT (18). SDT posits the three needs that are associated with IM: competence, (personal) relatedness, and autonomy. SDT shows how behavior's regulatory style differs from external regulation to intrinsic regulation (IM). In NEAR, patients are encouraged to regulate behaviors in multiple ways (i.e., external vs. internal), in cognitive tasks and intervention techniques; it was shown that intervention that incorporated SDT improved cognition larger compared to intervention that did not (8).

Analogous to learning in an educational setting, people engage in tasks based on expectancy-value theory in psychiatric rehabilitation (19). It is said that people tend to engage in new behavior (and for most patients in CR, working on cognitive tasks is new behavior) when they feel in control, autonomous, competent, efficacious, and when they find the behavior interesting or meaningful. To address these issues and to ultimately enhance IM so that people with psychiatric illness can develop autonomous help-seeking behaviors, NEAR incorporates motivation enhancing components in cognitive tasks and intervention techniques.

NEAR uses both restorative and compensatory approaches. Intervention techniques include errorless learning, shaping, and prompting (12). Errorless learning introduces a task at a certain difficulty level only after easier levels are mastered, so that chances for making errors are limited. Shaping enables goal attainment as it presents with achievable, non-threatening, small goals. In prompting, facilitator may suggest what behaviors to take without giving the answers. The interventions are different from providing the answer, as it gives the patient a chance to solve the task themselves.

The techniques make it possible for patients to engage in tasks autonomously. NEAR facilitators act like a coach for athletes using these techniques: while they may show how to solve a problem, they typically do not provide the answers. NEAR cognitive tasks may be contextualized in life so that trained cognition may be easily transferred to real life situations.

NEAR facilitates a verbal session in addition to a cognitive session. Verbal session is also referred to as bridging session, as it bridges cognitive tasks to real life cognition, or life goals such as vocational goal. Bridging session purports to transfer of cognitive skills trained in cognitive sessions to real-life situations. Bridging session may take a form of a discussion that allows participants present or learn about types of cognitive tasks they are working on, or a group game which allows participants to use cognitive skills they are training, or a group session with emphasis on communication. For instance, a patient may recall a memory task from a cognitive session and make a connection to real life by stating that he/she must memorize item placements and pricing at work.

Cognitive remediation outcome has been reported from meta-analyses. Interested readers are suggested to refer to meta-analyses that compare the outcomes of different CR methods (19, 20). A meta-analysis of 26 CR outcome studies revealed improvement of cognition with medium effect size of 0.41 (21). NEAR has improved cognition such as attention (8), processing speed (21, 22), immediate learning and memory (1), and delayed verbal memory (22). NEAR outcome studies have been conducted at a variety of settings such as outpatient psychiatric facilities (1, 13), inpatient psychiatric units (4), intensive psychiatric rehabilitation (23), supportive housing facility (24), and its controlled trials have been conducted (3, 13): in these studies, computer sessions were provided once or twice a week, and the duration of the treatment differed from 4 to 15 weeks. Longer treatment duration is recommended to achieve clinically significant change (12). Outcome studies do not clarify whether verbal session was conducted.

Cognitive remediation has been known to be most effective when combined with a comprehensive psychiatric rehabilitation (25), and when drill-and-practice coaching is combined with strategy coaching (21). CR may be provided as a part of a more comprehensive psychiatric rehabilitation, such as psychiatric day treatment. Neurocognition may be trained in CR while the skills connected to the same domain may be practiced in other programs such as farming, cooking, or athletic sports. In a CR program such as NEAR, patients have a chance to practice certain skill repeatedly, just as one might practice striking a baseball, while they also have a chance to strategize their approach to a cognitive task.

Patient factors known to be associated with CR outcomes include baseline cognition, clinical stability (26), motivation (25), and phase of illness (27). Severity of positive or negative symptoms, provided pharmacological treatment is provided, does not seem to affect their eligibility for CR. It seems to stand for a reason that a strong motivation as measured by attendance rate was positively associated with improvement in cognition (25). Motivational interviewing has also been conducted prior to patients' enrollment in CR (28). CR outcome studies divided the patients depending on the phase of illness consisting of early course and chronic phase. Early-course patients, when compared to chronic patients, mostly showed larger improvement in cognition (27), but the reasoning behind the difference is yet to be determined.

Limitations of CR outcome studies are listed here, providing their future directions. Overlap of treatment providers and evaluators may crowd the outcome evaluation. Variability of control conditions makes it difficult to determine the effectiveness of intervention among different trials. CR treatment fidelity is not clearly established in some studies, making it difficult to know specificity of how CR was provided. Variability of outcome scales makes it difficult to compare effectiveness of CR among different trials. Providing a specific manner which ascertains treatment fidelity is needed to improve the quality of CR outcome studies, while also enhancing optimal CR in clinical settings.

AUTHOR CONTRIBUTIONS

The author conceptualized and wrote this manuscript.

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Cognitive Remediation in Middle-Aged or Older Inpatients with Chronic Schizophrenia: A Randomized Controlled Trial in Korea

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Background: Accumulating evidence indicates that cognitive remediation (CR) is effective for improving various cognitive deficits in adult patients with schizophrenia. Although reports of brain plasticity in older adults and the service needs for chronic patients with schizophrenia are increasing, very few randomized controlled trials of CR have been conducted in middle-aged or older inpatients with chronic schizophrenia. We investigated the efficacy of individualized CR on the cognitive impairments of middle-aged or older inpatients with chronic schizophrenia within the context of comprehensive psychiatric rehabilitation (PR) by comparing the results obtained with PR only and treatment as usual (TAU).

Method: Fifty-seven middle-aged and older individuals with chronic schizophrenia and mild to moderate cognitive deficits were enrolled. Thirty-eight who were undergoing PR were randomly assigned to CR + PR ($N = 19$) or PR-only ($N = 19$) groups. Nineteen participants who were undergoing TAU without CR or PR were evaluated pre- and post-treatment.

Results: CR was easily provided and well received (drop-out rates = 5.3%) by middle-aged or older psychiatric inpatients. Compared to the PR-Only or TAU patients, patients in the CR + PR group showed greater improvement in executive functioning. Compared to TAU patients, CR + PR and PR-only patients showed greater improvement in logical memory. More patients in the CR + PR group improved clinically significantly in executive functioning and logical memory, compared with the PR-only and TAU patients.

Conclusions: These results suggested that CR improved some cognitive deficits in middle-aged or older inpatients with chronic schizophrenia and that it was effective as an adjunctive treatment to the usual PR services provided in inpatient settings.

Clinical Registration: KCT0002609

Keywords: cognitive remediation, older patients, brain plasticity, schizophrenia, inpatient psychiatric rehabilitation

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INTRODUCTION

Cognitive deficits have been identified as a key predictor of the functioning of patients with schizophrenia across various phases of the illness from the first episode to chronic illness, even after considering the patients' psychiatric symptoms (Green, 1996; Green and Nuechterlein, 1999; Green et al., 2004; Kurtz et al., 2005; Keefe et al., 2006; Rund et al., 2007). Cognitive functioning has critical therapeutic implications in diverse contexts, including treatment (Smith et al., 1999; Lysaker and Buck, 2007), and vocational rehabilitation (Bell et al., 2007, 2014; McGurk et al., 2015).

Given the therapeutic and functional importance of cognitive deficits in this population (Keefe and Harvey, 2012), cognitive remediation (CR) has received substantial attention as an adjunct treatment option for psychiatric rehabilitation (PR) (Wykes and Spaulding, 2011). In recent decades, randomized controlled trials (RCTs) have demonstrated the efficacy of CR on psychiatric symptoms, cognition, and functioning (Krabbendam and Aleman, 2003; McGurk et al., 2007a; Grynszpan et al., 2011; Wykes et al., 2011).

With the recent increases in life expectancy, the service needs for chronic mid-aged or older adults with chronic schizophrenia are growing (Granholm et al., 2005; Bartels et al., 2014; Schoepf et al., 2014). Cognitive function is responsible for functional competence even after considering key demographic information, such as age and education, and the anticholinergic burden of medications, in older adults with schizophrenia (Tsoutsoulas et al., 2016).

Even though older adults have brain plasticity (Willis et al., 2006; Boron et al., 2007), it is unclear whether CR is effective in middle-aged or older adults with or without schizophrenia (Kontis et al., 2013) or the benefits of CR are also produced by untrained cognitive tasks (Owen et al., 2010).

Even though CR has been reported as more beneficial to younger patients with schizophrenia compared to mid-aged or older patients with schizophrenia (McGurk and Mueser, 2008; Kontis et al., 2013), several studies have indicated that CR still has benefits for in mid-aged or older patients. Wykes and colleagues (Wykes et al., 2007) have reported that, after approximately 30 h of cognitive training, patients who were 40 or older had similar improvements in their memory as those shown by patients younger than 40. Bowie et al. (2014) have reported that older patients (mean age, 45.4) showed improvements in verbal memory and verbal fluency as younger patients (mean age, 28.1) did, while only the younger patients had improvements in processing speed and executive functioning. Most recently, Corbera et al. (2017) conducted a secondary analysis of the results of three different RCTs to investigate the responses of patients with three different age ranges (i.e., <26, between 26 and 39, and over 40) to CR treatment, and they reported that the younger patients benefited more (trend level of significance) compared with the older patient group.

Because promising findings have been reported in non-RCTs, a RCT of the role of CR in the treatment of the cognitive functioning of middle-aged or older patients with schizophrenia is still needed. Sharma et al. (2016) highlighted in their review that controlled studies are needed to better understand whether CR benefits older adults with severe mental illness within the context of broad PR treatments, even though CR appears to have therapeutic benefits for older adults with various health conditions, such as mild cognitive impairment, brain injury, and severe mental illness (Bartels and Pratt, 2009).

To the best of our knowledge, only one RCT study has been conducted to date in middle-aged or older out-patients with schizophrenia (mean age, 46.9 and 48.5 for CR and Control, respectively), and it reported null effects in the neuropsychological assessments of the outpatients compared to active control groups (Dickinson et al., 2010). Since Spaulding et al. (1999a)'s seminal work on CR for inpatients with schizophrenia during intensive PR, numerous RCT trials have demonstrated its clinical effectiveness and functional importance for recovery of relatively younger inpatients with schizophrenia (Medalia et al., 1998, 2000, 2001; Sartory et al., 2005; Silverstein et al., 2005, 2009; Ueland and Rund, 2005; Vauth et al., 2005; Wykes et al., 2007). Despite the growing number of chronic and older inpatients with schizophrenia, only one RCT has been conducted on CR in relatively older in-patients (mean age, 43.46), and its findings suggested that CR results in additional benefits within the context of vocational rehabilitation (Lindenmayer et al., 2008). Previous meta-analyses (McGurk et al., 2007b; Wykes et al., 2011) have emphasized that investigations of whether CR has additive benefits in older patients with schizophrenia within the context of PR are of great interest (Bartels and Pratt, 2009; Sharma et al., 2016).

To examine the effects of CR and PR together and PR only on neurocognitive functioning and psychiatric symptoms in this study, we included a treatment-as-usual (TAU) group (without PR) as another control group. Importantly, to the best of our knowledge, no RCTs have been conducted on non-western inpatients within the context of comprehensive PR, even though inpatient clinics, in conjunction with community-based PR, are important settings for PR.

Thus, in the current study, we employed a RCT design (CR + PR vs. PR only) to evaluate the efficacy of a CR program for middle-aged or older inpatients with chronic schizophrenia within a PR context compared to TAU. We hypothesized that CR + PR treatment would result in the greatest improvements, followed by PR only and TAU, in untrained neurocognitive domains and psychiatric symptoms in middle-aged or older inpatients with chronic schizophrenia.

Abbreviations: CL, Conceptual level; CR, Cognitive remediation; LM, Logical memory; PANSS, Positive and negative syndrome scale; PR, Psychiatric rehabilitation; RCI, Reliable change index; RCTs, Randomized controlled trials; TAU, Treatment as usual; WAIS-IV, Wechsler Adult Intelligence Scale-Fourth edition; WCST, Wisconsin card sorting test; WMS-IV, Wechsler Memory Scale-Fourth Edition.

METHODS

Clinical Trial Design

Of the 79 inpatients with schizophrenia who were referred to this clinical trial (53 from the PR unit and 26 from the TAU unit), eight did not meet the inclusion criteria and 14 declined

to participate. A final total of 38 inpatients with schizophrenia from the PR unit who met the inclusion criteria of the study and who gave consent were randomly assigned to the CR + PR or PR-only groups (**Figure 1**). Nineteen inpatients with schizophrenia from the TAU unit were allocated to the TAU group (**Figure 1**). The participants from the PR unit who met the study criteria and consented to the current trial were informed that they were assigned to CR in addition to the usual PR programs or the usual PR program only. The TAU group was informed that they would be assessed two different times. All participants were interviewed and assessed before starting the trial and immediately after the trial. Positive and Negative Syndrome Scale (PANSS) and neurocognitive assessments were conducted by master-level pretrained research assistants. The administration and scoring procedures were supervised by licensed clinical psychologists (K. H. Choi, W. H. Lee, and S. Choi). The current study has been registered with Clinical Research Information Service (CRIS) registry, number KCT0002609.

Participants

The diagnoses of the 57 inpatients with schizophrenia (32 males and 25 females) were confirmed by the Structured Clinical Interview for DSM-IV Axis I disorders (American Psychiatric Association, 1994). Prior to the very recent reform in "Acts on the Improvement of Mental Health and the Support for Welfare Services for Mental Patients" in Korea, the average percentage of involuntary hospitalization to mental health units in Korea has been very high from 67.9 to 93.3% (Ministry of Health Welfare, 2016). All participants in this study were involuntarily admitted to the long stay close unit of the hospital. The mean age of the patients was 50.07, with a range of 36–59, and their number of years of education was 10.93. All patients had been on stable medication regimens for the previous 30 days, with no groups differed for psychotropic medication dose equivalents (Inada and Inagaki, 2015) and maintained their medication dosages during the current 3-month long outcome trial, except for PRN medications. Participants were excluded if they had any of the following: substance use, serious traumatic brain injury or other neurological disorder, or acute psychiatric symptoms. Four patients were dropped due to discharge. All participants in this research voluntarily participated and provided written informed consent.

Measures

Psychiatric Symptoms

Psychiatric symptoms were measured by using the PANSS (Kay et al., 1987), which includes five subscales: negative, excitement, cognitive, positive, and depressive (Bell et al., 1994). The internal consistency coefficients of the original version of each subscale were the following: negative ($\alpha = 0.86$), excitement ($\alpha = 0.76$), cognitive ($\alpha = 0.79$), positive ($\alpha = 0.80$), and depressive ($\alpha = 0.69$). In the current study, the internal consistency coefficients were of each subscale were the following: negative ($\alpha = 0.92$), excitement ($\alpha = 0.45$), cognitive ($\alpha = 0.43$), positive ($\alpha = 0.74$), and depressive ($\alpha = 0.67$). In the current study, the inter-rater reliability coefficient was 0.96.

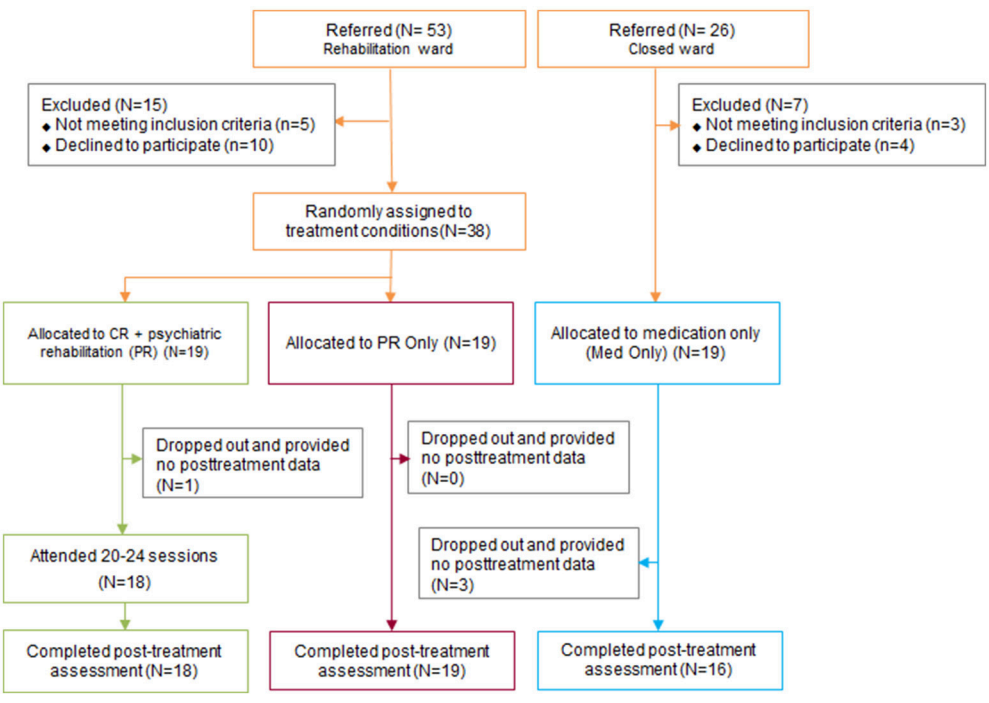

FIGURE 1 | Consolidated standards of reporting trials diagram of the selection of the participants in the study. CR, Cognitive remediation; PR, Psychiatric rehabilitation; TAU, Treatment As Usual.

Motivation

Participants' overall motivation was measured by the BIS/BAS scale (Carver and White, 1994; Kim and Kim, 2001).

Premorbid IQ

Premorbid IQ was estimated by using the Information subtest score from the Wechsler Adult Intelligence Scale-Fourth edition (WAIS-IV) (Wechsler, 2008) and demographic variables, including years of education, age, gender, and ethnicity (Kim et al., 2015).

Neurocognition

Attention/processing speed was assessed by using the Trail Making Test A, which requires the examinee to draw a line between numbers in order within 360 s (Arbuthnott and Frank, 2000). Processing speed was also assessed by using the symbol-coding test, which is a subtest of the WAIS-IV (Wechsler, 2008) and which requires the conversion of numbers to matched symbols in a limited amount of time. Patients with schizophrenia exhibit decreased processing speed and working memory (Kreiner and Ryan, 2001).

Working memory was assessed by using the letter-number sequencing test, which is a subtest of the WAIS-IV (Wechsler, 2008) and which requires the manipulation or visualization of orally presented words and numbers and the recitation of the numbers first in numerical order and then letters in alphabetical order. Verbal logical memory (LM) was assessed by using the LM (I and II) tests, which are subtests of the Wechsler Memory Scale-Fourth Edition (WMS-IV) (Wechsler, 2009). The test is comprised of immediate recall, delayed recall, and recognition tasks for two stories. The stories are read with clear pronunciation by the examiner. The LM tests measure the examinees' verbal memory capacity, which is the ability to recall organized and meaningful linguistic information components.

Executive functioning was assessed by using the Trail Making Test B (Trails B), Wisconsin Card Sorting Test (WCST) 64, and Verbal Fluency Test. The Trails B requires the examinee to draw a line between numbers and letters that are scattered on paper following the given rules within 360 s (Arbuthnott and Frank, 2000). The WCST evaluates executive function, which is the essential cognitive function that enables goal setting, planning, and goal-directed behaviors. The WCST 64 consists of four stimulus cards and 64 response cards that have three different dimensions (i.e., form, color, and number), with each having four components. The examinee is required to place each response card under a stimulus card that they consider a match. After matching the cards, (s)he gets feedback on whether they were right or wrong. Because they are not given any instructions on the pairing rules, the examinees have to determine the rules from the feedback. The verbal fluency test requires the examinees to find as many words as possible that begin with a given consonant in a limited amount of time (60 s) (Lee et al., 2000).

CR

The CR treatment consisted of 24 sessions that occurred twice a week for 1 h/session for over 3 months. The PSSCogRehab software program (version 12.0; Psychological Software Services, Inc., Indianapolis, IN, USA) was translated in Korean by K. H. Choi's research group and then used for CR training (Bracy, 2012). The CR training was formulated to include practicing attention, memory, and executive functioning (**Figure 2**). The starting level and initial training schedules were determined for each individual by a therapist according to their pretreatment assessment. The training schedules (e.g., targeted neurocognitive domains, difficulty levels, etc.) were individualized and updated based on the participants' preferences and levels of performance. CR games from Lumosity.com were also employed to supplement the CR training for spatial memory (e.g., tile matrix and treasures on the beach) and executive functioning (e.g., color match and world of illusion). Because most participants in the current study were not familiar with using computers, the therapists introduced the basic skills (e.g., using a mouse) of computer usage at the initial session and then gradually moved to the CR tasks. The CR sessions consisted of computer-based CR training (50 min) and a bridging group session (10 min) (Medalia et al., 2009). To increase motivation, the participants were reminded at the beginning of each session of their goals for joining the CR program, and they were given the opportunity to link their personal goals with the CR training. In addition, the participants were able to choose tasks that they wanted to practice in each session with the clinician's assistance and monitor their progress. After about 50 min of computer-based CR training, the group members gathered for a bridging group (Medalia et al., 2009), in which they discussed the connections between their goals and the cognitive training and exchanged strategies. The therapists used motivational interviewing techniques to enhance the participants' intrinsic motivation toward the CR (Fiszdon et al., 2016; Lee et al., 2017). All CR sessions were reviewed by K. H. Choi in a weekly supervision meeting or *in vivo* training sessions to confirm the consistency of the CR protocol.

PR

The participants who were randomized to the CR + PR and PR-only groups received comprehensive inpatient PR, including optimal pharmacotherapy, vocational rehabilitation, social skills training, daily living skills training, illness management, independent living skills training, and patient empowerment program. The PR did not include specific training on neurocognitive functioning.

TAU

The participants who were recruited from the TAU unit received optimal pharmacotherapy, psychoeducation, socialization and recreational programs. The TAU group did not receive specific training on neurocognitive functioning or PR-specific components, such as vocational rehabilitation or skills training.

Data Analysis

A series of repeated-measures analyses of variance [within-subjects factor, time; between-subjects factor, group (CR + PR, PR only, or TAU)] were conducted to examine the effects of CR on the neurocognitive measures, psychiatric symptoms, and clinic unit behaviors. The effect sizes were calculated with the

	Training Emphases	Examples of Specific Training Exercises
First Session	• Engagement and rapport • Program and computer orientation • Motivation enhancement • Mouse skills training	
Attention Training	• Engagement and rapport (cont.) • Motivation enhancement (cont.) • Focused attention • Divided attention	• *Simple Visual/Auditory Reaction*: Click the screen when the visual/auditory stimulus is presented • *Simple Choice Visual Reaction*: Click the screen only when the target visual/auditory stimulus is presented, with random distracters presented
Memory Training	• Spatial memory • Working memory • Concentration	• *Digit & Graphic*: Memorize the presented sequential stimuli (digits or graphics) and recall them in order after pause. The order of recall can be forward or backward. • *Tile matrix**: Remember the colorized cells on 4x4 to 16x16 matrix. The number of cell on matrix increases when the colorized cells were identified correctly. • *Treasures on the beach**: Watch and memorize the graphics (treasures) on screen, and after the graphics are gone, distinguish items whether they were presented or not.
Executive Function Training	• Planning • Principle learning & applying • Effective performance • Inhibit responses	• *Color match**: Two colored words are presented on the screen and the participant have to respond whether the meani ng of the word on left side refers to the color of the word on right side or not. • *Pyramid*: There are three rods and a number of disks of different sizes. The participant have to move the disks from a rod to another with minimum movement. Only one disk can be moved at a time, and no disk can be placed over a smaller disk. • *World of Illusion**: Puzzle game that each piece has a colored symbol on it. The horizontal pieces have to be put by the piece with same figured symbol, the vertical pieces have to be put by the pieces with the same colored symbol.

• Participants were able to proceed to next task when they met pass-fail criteria for each task.
• Tasks indicated by star (*) refers to the exercises in Lumosity.

FIGURE 2 | Targeted domains and detailed training tasks in CR.

Time-by-Group interaction. *Post-hoc* analyses were conducted to compare the group means at each time point. To estimate the clinical significance, the reliable change index (RCI) was calculated and compared among the groups (Wise, 2004). The RCI was calculated as $\frac{X_1 - X_2}{SE}$ (X_1 = pretest score; X_2 = post-test score; $SE = s_1\sqrt{1 - r_{xx}}$; s_1 = the standard deviation of the control group, normal population, or pretreatment group; and r_{xx} = the test-retest reliability). RCI scores that were equal or >1.96 are considered reliable changes (Wise, 2004).

Power Analysis

Using G*Power (version 3.1.9.2, Heinrich Heine University, Düsseldorf, Germany) (i.e., repeated measures analyses of variance, measures at two-time points for three groups, $p < 0.05$, correlations = 0.5–0.8, and Cohen's $d = 0.58$ in the context of PR) (Faul et al., 2009), moderate effects were found in 45 participants. Considering the potential for missingness, we assigned 19 participants to each group.

Ethical Standards

The study was approved by both Yongin Mental Hospital Institutional Review Board and Korea University Institutional Review Board. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

RESULTS

As shown in **Table 1**, 38 participants were randomized to either the CR + PR or PR-only groups, and an additional 19 participants from the TAU unit were allocated to the TAU group. No group differences were found in key demographical variables (e.g., age, education, and gender ratio), premorbid IQ, psychiatric characteristics (e.g., age of onset, duration of illness, number of hospitalizations, BIS/BAS scores and PANSS

TABLE 1 | Demographic information.

	CR + PR	PR Only	TAU	*F*-value	Significance
	n = 19	*n* = 19	*n* = 19	Or χ^2	(*p*-value)
	M (SD)	M (SD)	M (SD)		
Age (years)	49.58 (6.19)	49.74 (6.07)	50.89 (6.00)	0.26	0.77
Education (years)	11.11 (3.14)	11.26 (3.72)	10.42 (2.69)	0.37	0.69
Gender, male (percentage)	63.16	52.63	52.63	0.57	0.75
Premorbid IQ estimate	94.37 (9.05)	97.55 (10.57)	93.92 (9.15)	0.80	0.45
Age of Onset	27.81 (7.31)	25.87 (6.84)	23.45 (6.86)	1.80	0.17
Duration of Illness	22.19 (10.66)	23.87 (7.94)	27.45 (5.89)	1.93	0.16
Number of Hospitalizations	5.05 (4.01)	4.67 (3.31)	6.37 (7.22)	0.59	0.58
PSYCHIATRIC SYMPTOMS					
PANSS					
Cognition	23.11 (6.26)	21.32 (3.96)	23.53 (5.58)	0.91	0.41
Depression/Anxiety	11.58 (5.23)	10.11 (4.19)	8.89 (2.98)	1.91	0.16
Excitement/Hostility	5.74 (1.88)	5.84 (1.68)	6.74 (2.21)	1.53	0.22
Negative	16.58 (5.43)	15.37 (5.96)	17.37 (7.22)	0.49	0.61
Positive	13.32 (6.28)	12.16 (5.04)	12.21 (4.39)	0.29	0.75
COGNITIVE FUNCTIONS (T SCORES)					
Processing Speed					
Coding	37.72 (11.11)	39.12 (13.19)	34.21 (10.71)	0.89	0.42
Attention					
TMT-A	52.67 (10.34)	55.02 (7.52)	48.67 (21.27)	0.96	0.39
Verbal Working Memory					
LNS	37.89 (14.19)	36.67 (9.36)	32.63 (12.75)	0.96	0.39
Verbal Memory					
LM I	32.98 (9.42)	36.67 (11.39)	31.93 (6.88)	1.33	0.27
LM II	31.4 (9.05)	33.33 (11.86)	28.07 (5.59)	1.59	0.21
Executive Function					
TMT-B	37.12 (14.1)	34.22 (12.96)	28.73 (10.19)	2.20	0.12
VFT	10.63 (3.53)	10.21 (3.05)	9.32 (2.87)	0.86	0.43
WCST TE	36.84 (11.3)	35.58 (12.33)	34.95 (10.11)	0.14	0.87
WCST %PE	40.13 (20.31)	34.52 (22.44)	35.78 (23.81)	0.33	0.72
WCST %CL	25.76 (22.78)	29.86 (22.23)	29.79 (18.19)	0.23	0.79
CPZ Equivalents	1243.79 (2772.51)	2517.99 (6048.33)	510.43 (487.78)	1.32	0.28
BIS/BAS					
Reward Responsiveness	14.16(2.77)	14.47(2.53)	13.74(2.79)	0.36	0.70
Drive	11.47(2.29)	10.89(2.23)	10.68(2.69)	0.55	0.58
Fun Seeking	9.89(2.38)	10.89(1.78)	9.26(2.49)	2.56	0.09
Behavioral Inhibition	18.63(2.85)	19.42(2.06)	19.21(3.19)	0.42	0.66

CR, Cognitive remediation; PR, Psychiatric rehabilitation; TAU, Treatment as usual; M, mean; SD, standard deviation; PANSS, Positive and Negative Syndrome Scale; TMT-A, Trail Making Test-A; LNS, Letter-Number Sequencing; LM I, Logical Memory I; LM II, Logical Memory II; TMT-B, Trail Making Test-B; VFT, Verbal fluency test; WCST TE, Wisconsin Card Sorting Test Total Errors; WCST %PE, Wisconsin Card Sorting Test Perseveration errors; WCST %CL, Wisconsin Card Sorting Test Conceptual level responses; CPZ, chlorpromazine.

scores), or baseline neurocognitive functioning (**Table 1**). The drop-out rates were low for the CR + PR (5.3%) and PR (0.0%) participants, while it was 15.8% for the TAU participants (**Figure 1**).

Effects of CR on Neurocognition

The data for all neurocognitive variables are presented in **Table 2**. The time (i.e., pre- and post-treatment) × group (i.e., CR + PR, PR only, and TAU) interactions were significant for both immediate recall ($p < 0.001$, $\eta_p^2 = 0.21$) and delayed recall ($p = 0.03$, $\eta_p^2 = 0.13$), with medium to large effect sizes. The total errors, perseverative errors, and conceptual level (CL) responses (%) were analyzed to observe abstract thinking, learning strategies, and cognitive flexibility. The time × group interactions were significant for WCST total errors ($p = 0.02$, $\eta_p^2 = 0.15$) and CL responses ($p = 0.004$, $\eta_p^2 = 0.20$), with medium to large effect sizes (**Table 2**). No group differences were found for processing speed (WAIS-IV

TABLE 2 | Effects of cognitive remediation on neurocognition.

Outcome measures		CR + PR		PR Only		TAU		Group × Time	ES
		n = 18		*n* = 19		*n* = 16		*p*-value	(η_p^2)
		Pre	Post	Pre	Post	Pre	Post		
		M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)		
PROCESSING SPEED									
	Coding	38.70 (10.55)	39.44 (11.73)	39.12 (13.19)	41.58 (14.20)	32.92 (10.81)	31.46 (8.52)	0.13	0.08
ATTENTION									
	TMT-A	52.81 (10.62)	55.58 (12.03)	55.02 (7.52)	57.76 (6.51)	47.98 (22.79)	46.00 (22.94)	0.52	0.03
VERBAL WORKING MEMORY									
	LNS	38.89 (13.91)	41.30 (10.91)	36.67 (9.36)	39.12 (10.23)	31.25 (13.44)	29.38 (10.63)	0.16	0.07
VERBAL MEMORY									
	LM I	33.15 (9.67)	41.30 (13.19)	36.67 (11.39)	37.02 (11.49)	32.08 (7.39)	29.79 (9.23)	<0.01	0.21
	LM II	31.85 (9.09)	40.37 (13.52)	33.33 (11.86)	35.61 (13.43)	27.71 (5.67)	28.75 (7.59)	0.03	0.13
EXECUTIVE FUNCTION									
	TMT-B	37.28 (14.49)	37.16 (14.36)	34.22 (12.96)	40.08 (9.31)	29.53 (10.33)	33.31 (11.15)	0.14	0.07
	VFT	10.83 (3.52)	10.83 (3.4)	10.21 (3.05)	10.79 (2.49)	9.00 (2.97)	9.69 (3.16)	0.59	0.02
	WCST TE	36.17 (11.23)	30.67 (12.33)	35.58 (12.33)	38.53 (8.74)	36.81 (9.57)	39.63 (9.79)	0.02	0.15
	WCST %PE	40.48 (20.84)	34.11 (21.99)	34.52 (22.44)	39.14 (20.94)	39.07 (24.56)	44.14 (24.07)	0.17	0.07
	WCST %CL	27.19 (22.54)	36.46 (25.62)	29.86 (22.23)	19.98 (16.15)	26.98 (17.69)	20.21 (17.38)	<0.01	0.20

CR, Cognitive remediation; PR, Psychiatric rehabilitation; TAU, Treatment as usual; ES, Effect size; η_p^2, Partial eta square; M, mean; SD, standard deviation; TMT-A, Trail Making Test-A; LNS, Letter-Number Sequencing; LM I, Logical Memory I; LM II, Logical Memory II; TMT-B, Trail Making Test-B; VFT, Verbal fluency test; WCST TE, Wisconsin Card Sorting Test Total Errors; WCST %PE, Wisconsin Card Sorting Test Perseveration errors; WCST %CL, Wisconsin Card Sorting Test Conceptual level responses.

Coding), attention (TMT-A), verbal working memory (WAIS-IV Letter-Number Sequencing), or cognitive flexibility (WCST perseveration errors).

Least Significant Difference *post-hoc* tests were conducted on the variables with significant time × group interactions (i.e., LM I & II, WCST total errors, and WCST %CL) to investigate whether the groups differed at post-treatment (Supplemental Tables 1, 2). The CR + PR group showed greater post-treatment performance on both LM I and II compared with the performance of the TAU group (LM I: mean difference = 11.50, $p = 0.005$; LM II: mean difference = 11.62, $p = 0.007$), while the CR + PR and PR-only groups did not differ in both LM I and II. The PR-only group showed greater performance at a trend level of significance compared with the TAU group (LM I: mean difference = 7.23, $p = 0.070$; LM II: mean difference = 6.86, $p = 0.098$).

In addition, the CR + PR group showed greater post-treatment performance on both WCST total errors and WCST %CL compared with the PR-only group (WCST total errors: mean difference = 12.28, $p = 0.026$; WCST %CL: mean difference = 16.47, $p = 0.017$) and TAU group (WCST total errors: mean difference = 14.00, $p = 0.015$; WCST %CL: mean difference = 16.24, $p = 0.023$). However, no group differences were found on WCST total errors and WCST %CL between the PR-only and TAU groups (**Figure 3**).

Effects of CR in Psychiatric Symptoms

No significant group differences were observed for psychiatric symptoms (PANSS scores) (**Table 3**).

RCI

The RCIs were calculated for LM I and II, WCST total errors, and WCST %CL, which showed significant time × group interactions. As recommended by Wise (Wise, 2004), RCI scores ≥1.96 were considered reliable changes. As shown in **Figure 4**, more participants in the CR + PR group showed clinically significant improvements for the LM I (CR + PR: 7 participants; PR only: 1 participant; TAU: 2 participants) and LM II (CR + PR: 6 participants; PR only: 2 participants; TAU: 2 participants) (LM I: $\chi^2 = 8.35$, $p = 0.02$; LM II: $\chi^2 = 6.92$, $p = 0.03$). Differences with trend levels of significance were found for WCST total errors (CR + PR: 4 participants; PR only: 0 participants; TAU: 1 participant) and WCST %CL (CR + PR: 3 participants; PR only: 0 participants; TAU: 0 participants) (WCST total errors: $\chi^2 = 5.18$, $p = 0.08$; WCST %CL: $\chi^2 = 5.67$, $p = 0.06$).

DISCUSSION

The current study aimed to investigate whether CR treatment within the context of PR treatment (CR + PR) would produce meaningful improvements in neurocognition and psychiatric symptoms in middle-aged or older inpatients with chronic schizophrenia compared to either the PR-only or TAU group. For the CR, we employed a highly personalized and computerized CR protocol with motivational enhancements through a bridging group and motivational interviewing. To the best of our knowledge, the current study is the first RCT of middle-aged or older inpatients with chronic schizophrenia compared with

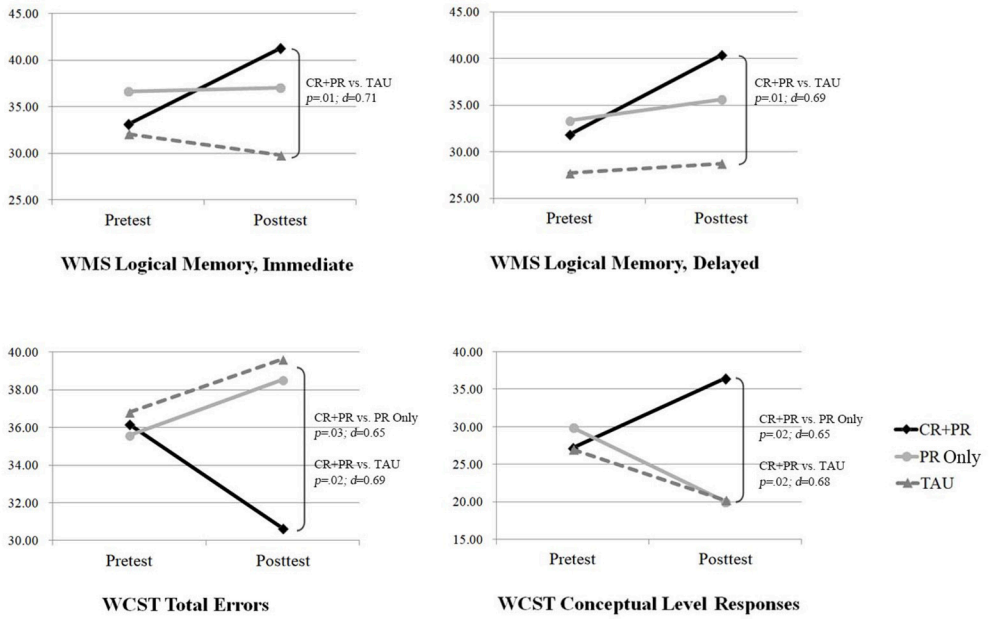

FIGURE 3 | Effects of CR on logical memory and executive functioning.

TABLE 3 | Effects of cognitive remediation on psychiatric symptoms.

Psychiatric symptoms	CR + PR		PR Only		TAU		Group × Time	ES
	n = 18		*n* = 19		*n* = 16		*p*-value	(η_p^2)
	Pre	Post	Pre	Post	Pre	Post		
	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)		
PANSS								
Cognition	23.11 (6.26)	22.79 (8.03)	21.32 (3.96)	22.42 (4.57)	23.53 (5.58)	21.58 (11.98)	0.56	0.02
Depression/Anxiety	11.58 (5.23)	9.42 (4.82)	10.11 (4.19)	9.84 (3.2)	8.89 (2.98)	8.26 (4.93)	0.44	0.03
Excitement/Hostility	5.74 (1.88)	5.95 (2.44)	5.84 (1.68)	6.05 (1.9)	6.74 (2.21)	6.95 (4.36)	1.00	0.00
Negative	16.58 (5.43)	15.58 (7.43)	15.37 (5.96)	19.05 (6.07)	17.37 (7.22)	17.68 (10.07)	0.12	0.08
Positive	13.32 (6.28)	12.26 (6.13)	12.16 (5.04)	12.53 (5.49)	12.21 (4.39)	11.05 (6.32)	0.58	0.02

CR, Cognitive remediation; PR, Psychiatric rehabilitation; TAU, Treatment as usual; ES, Effect size; η_p^2, Partial eta square; M, mean; SD, standard deviation; PANSS, Positive and Negative Syndrome Scale.

PR-only and TAU groups, especially conducted in a non-western country.

The results of the current study partially supported our primary hypothesis. Specifically, compared with the PR-only and TAU groups, the CR + PR group showed greater improvement in executive functioning (e.g., abstract thinking and learning strategies). In addition, the CR + PR group showed greater improvements in immediate and delayed LM compared with the TAU group but not the PR-only group. The PR-only group also showed greater improvements in immediate and delayed LM compared with the TAU group. The PR group improved more in executive functioning than the TAU did, but the difference was not reach significant. Importantly, the RCIs indicated that more participants in the CR + PR group had clinically meaningful improvements in LM and executive functioning compared with participants in the PR-only and TAU groups. However, since TAU group was not randomly assigned, the differences between "CR+PR vs. TAU" or "PR-only vs. TAU" should not be interpreted as causation.

These findings suggest that CR has additional treatment benefits for executive-level operation when it is delivered within a larger context of PR compared with PR only. Inpatient PR has nonspecific treatment effects on neuropsychological functioning, even without explicit CR training (Spaulding et al., 1999b). In addition to the nonspecific treatment effects of PR, CR effectively stimulates neurocognition to synergistically accelerate the benefits of PR.

No group differences were found in other neurocognitive domains or psychiatric symptoms. The pattern of treatment

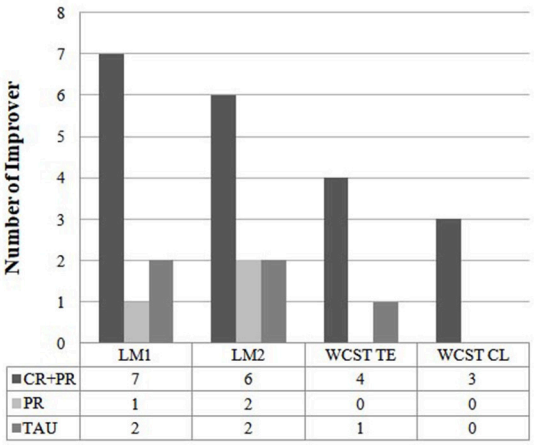

FIGURE 4 | Comparisons of the number of participants with meaningful improvement.

gains found in the current study was somewhat similar to the results of a previous controlled outcome trial that targeted younger patients in a comprehensive and intensive inpatient PR setting (Spaulding et al., 1999a) and that reported significant treatment gains in Card Sort random errors but not perseverative errors, Trails B, and PANSS total and subscales. The null effects of CR in other neurocognitive domains and psychiatric symptoms could be interpreted in several ways. All participants in the current trial received optimal pharmacotherapy, supportive therapies, and case management, which resulted in nonspecific treatment gains in neurocognition and/or psychiatric symptoms. In addition, the relatively low dose of CR (i.e., 24 sessions, twice per week) and small sample (i.e., 19 per group) in the current study might have resulted in insufficient power for detecting any potential treatment gains.

Comparing the current findings with the results of a previous RCT that was conducted in outpatients with similar ages (Dickinson et al., 2010) shows that, unlike the previous study, the current study found treatment gains in untrained neuropsychological assessments (i.e., executive functioning). Important differences between these two studies need to be acknowledged when interpreting the results. First, the patients examined in the current study were chronic inpatients who participated in the usual inpatient PR-only (without CR) and TAU units. Compared to outpatient clinics, inpatient settings have less cognitive stimulation. Thus, the addition of CR to inpatient PR might result in additional improvements in neuropsychological assessments compared with control conditions. Second, unlike Dickinson et al. (2010), we did not include active computer skills training as a control condition, and this might have resulted in greater differences between the CR + PR and PR-only groups in our study compared with those in the study by Dickinson et al. (2010).

The effects of CR on the neuropsychological assessments in the middle-aged or older inpatients with chronic schizophrenia in the current study were in line with the outcomes of previous CR studies. Bowie et al. have reported that both younger (early-course group) and older outpatients (longer-course group) with schizophrenia improved in working memory (digit sequencing) and executive functioning (Tower of London), but only the improvements in the early-course group in executive functioning were statistically significant and the improvements in working memory trended to significance. These findings suggested that older inpatients with schizophrenia maintain neuronal plasticity. Thus, CR should be considered as an adjunct treatment to usual PR services.

This study had several limitations. The CR training sessions were designed to have a relatively low dose (i.e., 24 sessions, twice per week for about 3 months) due to the durations of inpatient hospitalizations. Even though the low CR dose was similar to those used in previous studies (van der Gaag et al., 2002; Lindenmayer et al., 2008), more intense CR training might have produced better treatment outcomes. We did not have follow-up assessments also because of the durations of inpatient hospitalizations. Thus, the durability of the treatment gains should be explored in an inpatient PR setting in a longer future study. We should also acknowledge that the half of our evaluators were not blinded completely in measuring psychiatric symptoms or neurocognition in this study. To minimize potential evaluators' bias, all evaluators were trained intensively to approximate a great inter-rater reliability. During the administration and scoring process, they were observed and supervised with verbatim process by licensed psychologists (KHC, WHL, SC). Nevertheless, the evaluators' bias cannot be negated. Importantly, even though our sample size was modest for detecting medium effects, the statistical power of this study might have been insufficient for detecting small to moderate treatment gains. Thus, additional studies with more patients and longer CR sessions should be conducted to attempt to replicate the current findings. Finally, the effects of such improvements in cognitive function on daily function or social functioning in the actual ward need further investigation.

Despite the limitations noted above, the results of the current study highlight the importance of delivering CR within a PR context to middle-aged or older inpatients with chronic schizophrenia, especially to improve their executive functioning, which is a critical factor for learning in PR and treatment (Green, 1996; Spaulding et al., 1999a; Bowie and Harvey, 2006).

AUTHOR CONTRIBUTIONS

K-HC, S-HL, and T-YH designed the study. K-HC wrote the first draft of the manuscript and supervised cognitive remediation sessions, S-MK and JK administered cognitive remediation. S-MK, JK, and KP undertook the statistical analysis. S-CP supervised participants' recruitment and administration of psychotropic medications during trials. W-HL and SC supervised neurocognitive and clinical

assessments. All the authors commented on the manuscript. All the authors contributed to and have approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2017.02364/full#supplementary-material

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REVIEW
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Neural Correlates for Intrinsic Motivational Deficits of Schizophrenia; Implications for Therapeutics of Cognitive Impairment

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The ultimate goal of the treatment of schizophrenia is recovery, a notion related to improvement of cognitive and social functioning. Cognitive remediation therapies (CRT), one of the most effective cognition enhancing methods, have been shown to moderately improve social functioning. For this purpose, intrinsic motivation, related to internal values such as interest and enjoyment, has been shown to play a key role. Although the impairment of intrinsic motivation is one of the characteristics of schizophrenia, its neural mechanisms remain unclear. This is related to the lack of feasible measures of intrinsic motivation, and its response to treatment. According to the self-determination theory (SDT), not only intrinsic motivation, but extrinsic motivation has been reported to enhance learning and memory in healthy subjects to some extent. This finding suggests the contribution of different types of motivation to potentiate the ability of the CRT to treat cognitive impairment of schizophrenia. In this paper, we provide a review of psychological characteristics, assessment methods, and neural correlates of intrinsic motivation in healthy subjects and patients with schizophrenia. Particularly, we focus on neuroimaging studies of intrinsic motivation, including our own. These considerations are relevant to enhancement of functional outcomes of schizophrenia.

Keywords: intrinsic motivation, cognitive remediation therapy, schizophrenia, lateral prefrontal cortex, striatum, self-determination theory, neuroimaging, social functioning

INTRODUCTION

The ultimate goal of the treatment of schizophrenia (SCZ) is recovery, a notion related to improvement of social functioning, such as employment, independent living, and interpersonal relations (1). Patients with SCZ generally show impairments of cognitive functions, e.g., verbal memory, verbal fluency, motor function, attention, working memory, and executive function. Importantly, cognitive impairments have been reported to deteriorate social functioning (1–3).

Although antipsychotic medications exert limited effects on cognitive functions (4, 5), cognitive remediation therapies (CRTs) (6, 7) and neuromodulation, such as repetitive transcranial magnetic stimulation (8) and transcranial direct current stimulation (9), have been reported to moderately improve them. CRTs represent a psychosocial intervention that aim to directly improve cognitive functions by inducing neuroplasticity (6, 7). To attain certain improvement in social functioning, it is recommended to include CRT in a comprehensive rehabilitation program along with other psychosocial treatments, such as social skills training and cognitive behavioral therapy. Recent evidence shows the importance of integrating intermediate factors, such as social cognitive function and motivation, with CRT to effectively promote social functioning (10). Motivation is generally subdivided into intrinsic and extrinsic ones. Intrinsic motivation is subject to internal values, such as interest and enjoyment (10, 11), whereas extrinsic motivation is generated by external factors, such as reward and punishment. Intrinsic, rather than extrinsic motivation is considered to play a key role in enhancing the effect of psychiatric rehabilitation.

Among several types of CRT, the Neuropsychological Educational Approach to Cognitive Remediation (NEAR), developed by Medalia and Choi (12), focuses on enhancing intrinsic motivation. The program includes a group session, which bridges the cognitive training with daily life (12, 13). To evaluate intrinsic motivation for the intervention, self-report measures of intrinsic motivation, such as the Intrinsic Motivation Inventory (IMI), have been developed based on the self-determination theory (SDT) (14). Previous studies indicate that the IMI modified for SCZ patients (IMI-SR) (15) reflects internal value of a specific task or activity (16–18). Monitoring intrinsic motivation during the CRT is critical to determine whether the intervention is effective for each patient and/or whether a modification is necessary. For example, Silverstein (19) reported that the increase in intrinsic motivation was positively correlated with improvement in social functioning. However, examinations of intrinsic motivation using a self-report scale, such as IMI, may not be accurate, because participants' answers may be influenced by response bias caused by social desirability and self-monitoring capacity. In fact, cognitive deficits of SCZ have been associated with decreased activity in the lateral prefrontal cortex (LPFC) (20, 21), which may lead to a poor self-monitoring capacity. Therefore, it is essential to develop objective scales to monitor intrinsic motivation, which are feasible in clinical settings. For this purpose, understanding the neural basis of intrinsic motivation is necessary.

In healthy subjects, not only intrinsic motivation, but also autonomous types of extrinsic motivation are important for enhancing learning and memory (22). This is based on the SDT, suggesting that motivation comprises of several steps in a continuum of relative autonomy. Most autonomous types of motivation are intrinsic in nature, while extrinsic motivation varies from autonomous to controlled ones. In the psychosocial therapy of patients with SCZ, enhancing autonomous types of extrinsic motivation may lead to greater improvement of cognitive and social functioning.

In this paper, we reviewed the literature on the following topics: (1) the definition of intrinsic motivation based on the SDT, (2) the assessment of intrinsic motivation, (3) the role for intrinsic motivation in the therapeutics of cognitive impairment and (4) the neural basis of intrinsic motivation. Specifically, we summarize some findings on the neural correlates of intrinsic motivation estimated by neuroimaging in healthy subjects and patients with SCZ.

DEFINITION OF INTRINSIC MOTIVATION BASED ON SELF-DETERMINATION THEORY

Ryan and Deci (22) defined intrinsic motivation as "the inherent tendency to seek out novelty and challenge, to explore and investigate, and to stretch and extend one's capacities." On the other hand, extrinsic motivation is affected by external control, such as acquisition of reward or avoidance of a punishment. Among several theories to explain intrinsic motivation, such as the empirical drive theory, psychodynamic drive theory, and effectance motivation (23), the SDT (22, 24) is considered comprehensive for understanding intrinsic motivation. The SDT, based on organismic and humanistic principles, proposes a multidimensional theory of motivation. It has been developed out of the idea that intrinsic and extrinsic reasons for behaving lead to differential levels of performance and well-being for individuals (14, 24). Specifically, intrinsic motivation is suggested to be more closely associated with better performance, persistence, and well-being, and more accurately predict the adjustment of behavior, compared to extrinsic motivation (22, 24).

Previous studies have reported that intrinsic motivation varies under different conditions (14). Events such as the provision of positive feedback (25–27) and choice (28) enhance intrinsic motivation, whereas negative feedback (29, 30), deadlines (31), extrinsic motivation (32, 33) and other external impositions (34) generally diminish intrinsic motivation. Particularly, the undermining effect is known to exist between intrinsic and extrinsic motivation. The SDT indicates it is essential to satisfy three basic psychological needs: autonomy, competence, and relatedness for enhancement of intrinsic motivation (22). The need for autonomy is the sense that one's behavior should be self-determined, and includes the desire to take responsibility for one's own actions. On the other hand, the need for competence means the desire to feel the confidence that "I could do it if I tried," and to prove oneself to others. Finally, the need for relatedness refers to the desire to build and maintain a good relationship with other people in the community, and to attain a sense of solidarity (22).

Although, motivation is traditionally subdivided into intrinsic and extrinsic motivation, it has been suggested that motivation is not fully explained by this dichotomy (22). For example, when a student studies a foreign language because it is a required course, his action is extrinsically motivated based on external control. When a student studies a foreign language for preparation to study abroad, it is also extrinsically motivated because the action

is desirable as a means of achieving goal, not solely for interest or enjoyment. These two examples are considered to illustrate different types of extrinsic motivation in terms of the degree of autonomy. In this way, extrinsic motivation can dynamically shift according to the degree of internalization, or the process of taking in a value.

Based on this background, the SDT proposes a dimensional representation of motivation that is comprised of several steps along a continuum of relative autonomy (22). **Figure 1A** illustrates six types of motivation in the continuum of SDT. Among them, intrinsic motivation is the most self-determined and autonomous motivation. Extrinsic motivation is subdivided into four types, according to the degree of autonomy. Of the four types, external regulation is considered the most controlled type (22) in which a behavior is motivated by external control (acquisition of a reward or avoidance of a punishment). For example, when a student is rated by the academic self-regulation questionnaire (SRQ-A) (35), "Why do I do my homework?", the answer "Because I'll get in trouble if I don't" exemplifies external regulation. Introjected regulation is also considered a controlled type whereby a person's behavior is motivated by goals such as avoiding shame or anxiety or to maintain pride (22). For example, a student would answer "Because I want the teacher to think I'm a good student" in the same question. On the other hand, the stage of "identified regulation" categorized as more autonomous, whereby an action is motivated because of its value toward a goal, not because it is enjoyable or interesting (22). For example, students answer "Because it's important for me to do my homework" in the same question. Finally, integrated regulation is considered to be the most autonomous among the extrinsic motivation subtypes. In this type, a person's action is motivated because it is desirable and natural to do it, not necessarily because it is enjoyable or interesting (22). For example, students would answer "Because I want to do my homework" in the same question. Identified regulation and integrated regulation are known to improve performance, decrease dropout, and enhance learning, relative to more controlled types of regulation (36). Moreover, as Deci and Ryan (22) noted, the autonomous types of extrinsic motivation have been associated with the greater task engagement, better performance, and more learning.

Although studies of SCZ have focused on the impairment of intrinsic motivation (16, 37), little is known about continuous motivation deficits based on the SDT. In this respect, Gard et al. (38) examined whether each type of motivation in patients with SCZ was different from that in healthy subjects using the Ecological Momentary Assessment, a semi-structured interview. Goal-driving motivation in each individual was rated on a scale of specific anchors (0–3), based on the participant's response to "What goal do you have in the coming few hours?" and "What is the most important reason for having this goal?" (38). They assessed intrinsic motivation on the basis of three psychological needs, and also analyzed extrinsic motivation by separating the requirements of a reward and avoidance of a punishment. They found that the need for relatedness and extrinsic motivation based on punishment was not different between SCZ patients and healthy subjects, although the former showed less need for autonomy and competency, and extrinsic motivation based on reward (38). **Figure 1B** summarize the continuum in the SDT.

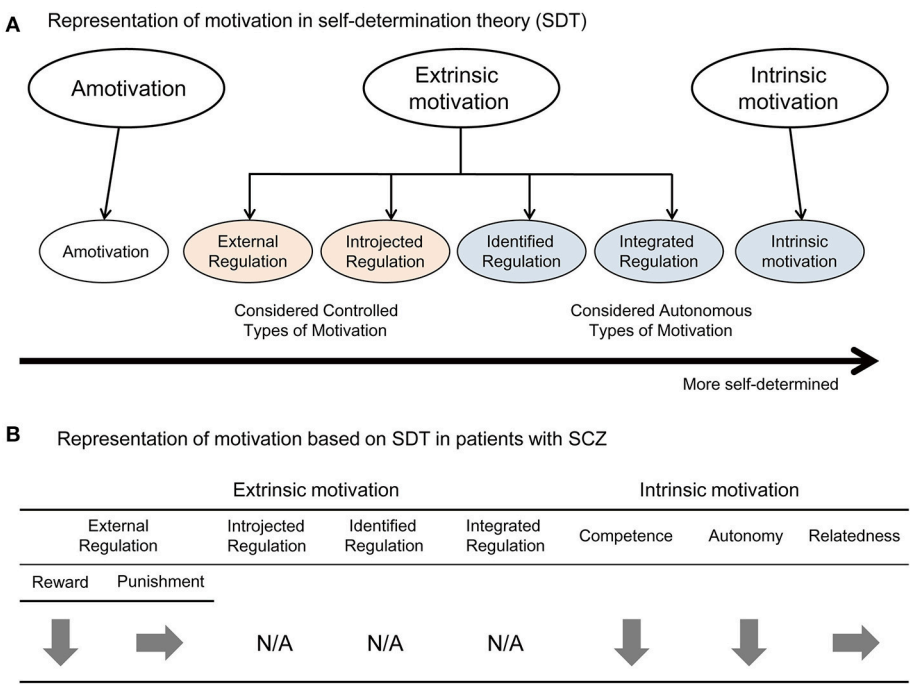

FIGURE 1 | (A) Representation of motivation in self-determination theory (SDT). This figure modified from Ryan and Deci (22). **(B)** Representation of motivation based on SDT in patients with SCZ. This shows data from Gard et al. (38) applied to the continuum in SDT.

Thus, people with SCZ may want to attain a good relationship with other people, which is hindered by impairment in social cognition, leading to the difficulty to link extrinsic reward to their actions (39, 40). This suggests that SCZ patients, perhaps due to repeated negative experiences, tend not to require extrinsic rewards and are sensitive to punishment (41).

In summary, it is important to develop treatment that enhances autonomy, competence, and sensitivity to extrinsic reward (38). Future studies will be required to understand which level of extrinsic motivation is impaired in SCZ, and how this relates to social functioning.

BEHAVIORAL ASSESSMENTS OF INTRINSIC MOTIVATION IN SCHIZOPHRENIA

The free-choice paradigm is known as a representative measurement of intrinsic motivation. In this paradigm, people can freely try different tasks, including a target task for a brief period when they believe nobody is observing their behavior. The number of trials during the free-choice period is used as an index of intrinsic motivation (32, 33). For example, Murayama et al. (42) developed the stopwatch (SW) task (**Figure 2A**). In this task, a SW appears on the monitor, and starts automatically; subjects are required to stop the SW within 50 ms of the 5-s time point by pressing a button (42). As a control task, they also used the watch-stop (WS) task, in which subjects press a button after the SW automatically stopped. A computer and a few booklets were set on the table in the room and participants could freely spend three minutes in this room (42). They could either play the SW or WS task, or read booklets as they like. Although subjects believed that nobody observed their behavior during this period, the number of trials was recorded by the computer program (42). By comparing the number of trials between the SW and WS tasks, the intrinsic motivation level was evaluated. The IMI is a self-report measurement of intrinsic motivation derived from the SDT (14). The IMI (27) comprises of 6 subscales (interest/enjoyment, effort, value/usefulness, pressure/tension, relatedness, and choice) and 54 items, and is effective for evaluating the level of intrinsic motivation for various activities, such as sports, school, medical procedures, and laboratory tasks (43–46).

Both measures described above have limitations (47). The results obtained from the free-choice paradigm may not always reflect intrinsic motivation because it is difficult to distinguish this from other processes such as persistence and preparing for future trials (47). Likewise, the self-report measures may not accurately capture the dynamic aspect of intrinsic motivation. Since participants are usually unable to report the intrinsic motivation during performance on a task, they are likely to report it afterwards on the basis of their memory (47). Based on these limitations, relatively few studies have measured both of them.

As discussed, little has been reported on the assessment of intrinsic motivation using the free-choice paradigm. On the other hand, Tobe et al. (48) used the General Causality Orientations Scale (GCOS) to examine the property of motivation in SCZ patients. This scale evaluates the degree of three types of orientation (autonomy, control, impersonal orientations) based on the SDT. Although scores on the control and impersonal orientations were not different between SCZ and healthy control groups, those on autonomy was significantly lower for the SCZ group compared to the control group. These findings suggest that the GCOS provides a valid measure to evaluate a declined of intrinsic motivation in SCZ patients. On the other hand, Choi et al. (15) modified the original IMI to assess the interventional effect of various psychosocial therapies in patients with SCZ, and named it IMI-SR. The IMI-SR consists of three subscales (interest and enjoyment, values, and choice) and a total of 21 questions (15). Previous studies indicate that the scale is effective to evaluate intrinsic motivation not only in association with the CRT, but also other trainings (15–18). However, participants' answers may be influenced by response bias caused by self-monitoring capacity.

ROLE OF INTRINSIC MOTIVATION IN THE THERAPEUTICS OF COGNITIVE IMPAIRMENT IN SCHIZOPHRENIA

In psychosocial therapies such as CRT, the balance of intrinsic motivation and extrinsic motivation to maximize the therapeutic effects is the critical issue. In SCZ, it has been shown that reward-based learning is ineffective because patients are less sensitive to positive feedback than are healthy controls (20, 49–51). On the other hand, when patients are intrinsically motivated to engage in a treatment program, they actively participate because they feel the activity itself is interesting and enjoyable (15). Therefore, it is critical to heighten the level of autonomy and self-efficacy, which support intrinsic motivation. Accordingly, Nakagami et al. (52) examined whether or not intrinsic motivation affects functional outcomes. They found that intrinsic motivation directly enhanced the neurocognitive improvement after CRT, and is an essential factor to improve social functioning (52). Moreover, they (53) showed that intrinsic motivation dynamically improves through the intervention, which was closely correlated with improvement in social functioning.

It is essential to enhance intrinsic motivation during the CRT. To enhance motivation, the bridging session is implemented, in which we try to link the training session to everyday activities. For example, the patients' group would discuss what benefit does training of spatial memory brings, and finally reach a conclusion that it is useful when we need to remember the location of an item on the shelf while working as a clerk. As this process aims to improve understanding the usefulness of the training, it does provoke autonomous types of extrinsic motivation, which are identified and/or integrated. Also, Silverstein (19) reported that extrinsic motivation is related to the improvement of cognitive impairment, and both intrinsic motivation and extrinsic motivation are essential for desirable outcomes in CRT. This finding is in line with the suggestion that extrinsic motivation may be critical to enhance the initiation of behavior, and to produce intrinsic motivation for maintaining it (19). Previous studies reported that extrinsic motivation, such as reward, are used in supportive interpersonal relations to promote

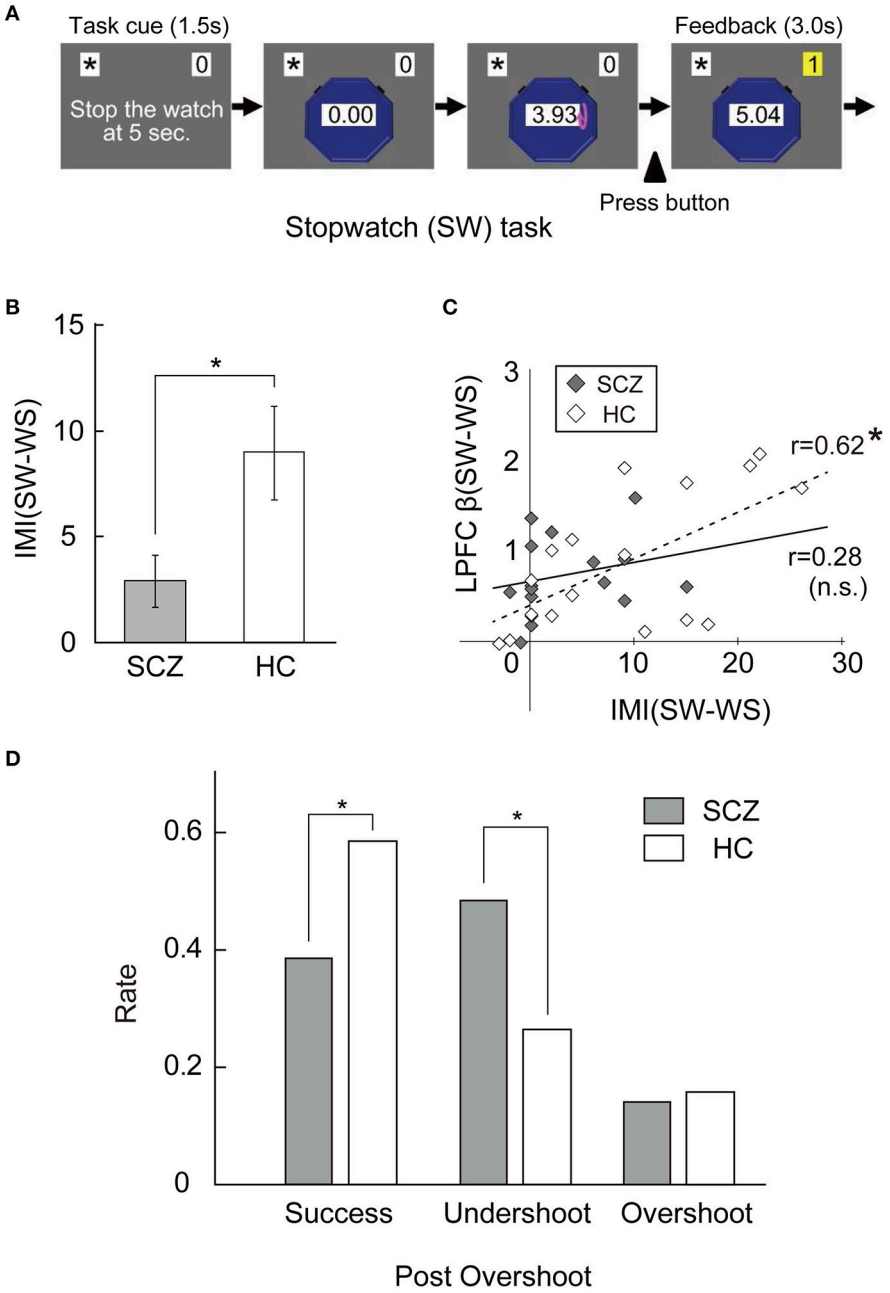

FIGURE 2 | (A) The stopwatch (SW) task. **(B)** The differences in IMI-SR between SW and WS tasks showed a significant between-group difference. (Mann–Whitney *U*-test, error bar: SEM, $*p < 0.05$). **(C)** In HC, the neural activity in LPFC was positively and significantly correlated with the index of intrinsic motivation, whereas not in SCZ. (Pearson, $*p < 0.0125$, n.s.: not significant). **(D)** Comparison of the performance level following the Overshoot between SCZ and HC. There was a significant main effect of Post-Overshoot (Success vs. Undershoot vs. Overshoot) ($p < 0.001$), and a significant interaction between Post-Overshoot and Group (SCZ vs. HC) ($p = 0.01$). The secondary analysis for each Post-Overshoot trial revealed a significant main effect of group for Success ($p = 0.01$) and Undershoot ($p = 0.01$). These figures modified from Takeda et al. (54).

the needs for competence and autonomy (55, 56). These items can be an integral component of cognitive enhancement techniques based on self-identified goals (57). In fact, positive outcomes related to extrinsic motivation are observed in learning (58) and treatment response (59). In addition, neural activity in brain areas related to cognitive function has been suggested to be modulated by anticipation and appearance of reward (49). Moreover, the undermining effect is observed if people are fully and intrinsically motivated to perform a specific activity and task, and adequately expect extrinsic reward. Since SCZ patients tend

to have relatively low intrinsic motivation, data from studies of the undermining effect in healthy subjects may be absent in SCZ patients (19). These considerations suggest that it may be worth incorporating extrinsic motivation such as reward into the CRT.

In summary, it will be essential to assess to what extent different types of extrinsic motivation, and intrinsic motivation are impaired in each patient for enhancing cognitive and social functioning.

NEURAL BASIS FOR INTRINSIC MOTIVATION IN SCHIZOPHRENIA

It is challenging to set up situations that lead participants to experience a sense of competence, i.e., manipulation of intrinsic motivation (60, 61). In recent neuroimaging studies, intrinsic motivation has been examined in various ways (**Table 1**).

Some studies have compared neural activity in intrinsically enjoyable game-like tasks and less enjoyable tasks. For example, Murayama et al. (42) observed that participants played the SW task more frequently than the WS task during the free-choice period, and found greater neural activity in the anterior striatum and LPFC during the SW task than the WS task. This finding suggests that these two areas constitute a neural system related to intrinsic motivation. Moreover, Murayama et al. (62) examined the neural mechanism related to self-determination by comparing neural activity during the SW task in two conditions. One was a self-determined-choice condition in which participants were freely required to select one of two SWs with different appearances, and the other was a forced-choice condition in which they were required to perform the SW task using an automatically designated SW (62). Whereas the activity of ventromedial prefrontal cortex (VMPFC) was markedly reduced in response to failure feedback compared to success feedback in the forced-choice trials, the activity levels were similarly high in the responses to the feedback between success and failure in the self-determined-choice trials. This suggests the neural activity in VMPFC is closely related to information processing regarding self-determination (62).

Kang et al. (63) investigated the neural mechanism related to curiosity by examining the relationship between neural activity when participants processed the trivia questions and the degree of curiosity about them. They found that activities in the caudate nucleus and LPFC were increased when participants experienced a higher level of curiosity, and that the increase of the activity in these brain areas was associated with improvement of memory (63). They pointed out that the caudate nucleus and LPFC are involved in memory encoding, and that intrinsic motivation is associated with enhanced learning (63). To assess more directly the relation between curiosity and learning, Gruber et al. (64) examined whether memory for task-relevant or for task-irrelevant information was improved depending on the level of curiosity by using trivia questions similar to those used by Kang (63). In this study, face stimuli were used as task-irrelevant information. When the level of curiosity was high, the recalls of both task-relevant and task-irrelevant information were improved. Moreover, they found that increased activation in the substantia nigra/ventral tegmental area (SN/VTA) and the hippocampus was related to the enhancement of memory (64). These findings indicate that the neural activity related to motivation that includes the striatum and LPFC (64, 65) may enhance the learning potential (60, 62–64, 66).

To determine whether the neural system of intrinsic motivation is different from that of extrinsic motivation, Lee's group (61, 67) proposed unique neural mechanisms related to intrinsic motivation. The authors compared neural activities when subjects imagined an action based on intrinsic motivation vs. those when they imagined the same action based on extrinsic motivation. They found that the anterior insular cortex (AIC) was activated to a greater extent in the intrinsic motivation situation compared to that of extrinsic motivation, suggesting that the AIC plays a role in intrinsic motivation (61, 67). Moreover, Lee and Reeve (68) examined neural activities when subjects actually performed the action based on intrinsic motivation in different levels of autonomy. They found that not only AIC but also the striatum was activated and that the functional connectivity between these brain areas was enhanced, suggesting that both brain regions are important for generating intrinsic motivation (68). The insular cortex plays a major role in processing emotion and feeling regardless of valence and integrating emotionally salient information and forming subjective emotional feelings (69, 70). The activity of the insular cortex was increased in performing self-generated behaviors compared with other behaviors (71, 72). In addition, its activity is related not only to who initiates and regulates certain behavior but also whether the behavior is generated from the "pure self" rather than from social influence (61, 67, 68).

In an electroencephalogram (EEG) study, Meng and Ma (73) examined the effect of autonomy using two time-estimation tasks with equal difficulty. In the choice condition, participants freely selected a time-estimation task, which requires subjects to indicate the end of the prespecified interval by pressing a button. In the no-choice condition, they performed the task automatically selected by a computer. They found a larger feedback-related negativity (FRN) in the choice condition compared to the no-choice condition. Moreover, Jin et al. (74) investigated the neural basis of intrinsic motivation by examining the neural disparity between the SW and WS tasks using event-related potentials. In the task cue period, the N2 amplitude in the SW task was smaller than that in the WS task. In the outcome period, smaller FRN amplitudes and lager P300 amplitudes were observed in the SW task compared to those in the WS task. Although the findings about the FRN in the two studies somewhat contradict with each other, they suggest that intrinsic motivation is measurable by means of event-related potentials, such as N2, FRN, and P300.

To clarify the neural mechanism of intrinsic motivation impairment in people with SCZ, we studied the neural activity in the striatum and LPFC of SCZ patients while they performed the SW task (**Figure 2A**) (54). Specifically, we compared the brain activity measured by fMRI and behavioral data between SCZ patients and healthy control (HC) participants (54). Firstly, scores of IMI-SR in the two tasks showed a significant between-group difference, so that people with SCZ were less intrinsically

TABLE 1 | Studies in neural correlates of intrinsic motivation using fMRI.

Study	Subjects	Sources of intrinsic motivation	Task	Paradigm and data detection	Related brain area
*(42)	HC: 28	Interest and enjoyment	Game like task (i.e., stopwatch task)	In the stopwatch (SW) task, subjects are required to stop the SW by pressing a button by myself. In the control task, subjects only need to press a button after a SW automatically stopped. The SW task is more interesting than the control task. They compared the activity during task cue period that indicates which of the two tasks will be displayed.	Striatum LPFC
(62)	HC: 35	Self-determination	Game like task (i.e., stopwatch task)	In self-determined-choice condition, participants performed the SW task by selecting freely one of two SWs with different appearances. In forced-choice condition, participants performed the SW task using an automatically designated SW. They compared the activity during the feedback period after the button press between success and failure in each condition.	MPFC
(63)	HC:19	Curiosity	Game like task (i.e., trivia questions)	Participants was presented the trivia questions. After they read them, they reported the level of curiosity of them. Authors examined the activity during the presentation period of the trivia questions by the difference of the level of curiosity.	Striatum LPFC
(64)	HC:24	Curiosity	Game like task (i.e., trivia questions)	After the trivia question was presented, participants anticipated the presentation of the answer. They investigated the activity during the anticipation period by the difference of the level of curiosity	Substantia nigra/ventral tegmental area
(67)	HC:10	Interest and enjoyment	Game like task (i.e. reading situation regarding IM and EM)	One of three phases (IM, EM, and Neutral) was selected. Participants read the selected phase of situation and replied by pressing a button whether they want to do it. Authors compared the activity during the presentation of the situation between IM and EM phase.	AIC
(61)	HC:16	Interest and enjoyment	Game like task (i.e. reading situation regarding IM and EM)	One of three phases (IM, EM, and Neutral) was selected. Participants read the selected phase of situation and reported how much they want to engage in it. Authors compared the activity during the presentation of the situation between IM and EM phase.	AIC
(68)	HC:22	Curiosity	Game like task (i.e., curiosity-inducing questions)	Participants were presented randomly selected question, and was asked to think of the correct answer, and reported how interesting the question or anagram was. Authors compared the activity during the presentation of the question between curiosity-inducing question and non-curiosity-inducing question.	Striatum AIC
(54)	SCZ:18 HC:17	Interest and enjoyment	Game like task (i.e., stopwatch task)	In the stopwatch (SW) task, subjects are required to stop the SW by pressing a button by myself. In the control task, subjects only need to press a button after a SW automatically stopped. The SW task is more interesting than the control task. We examined the activity during task cue period that indicates which of the two tasks will be displayed.	Striatum LPFC

*HC, Healthy control; SCZ, schizophrenia; IM, intrinsic motivation; EM, extrinsic motivation; LPFC, Lateral prefrontal cortex; MPFC, Medial prefrontal cortex; AIC, Anterior insular cortex. *Although Murayama et al. (42) examined the neural basis of the undermining effect, they also found the brain area related to intrinsic motivation in control group.*

motivated for the SW task (**Figure 2B**) (54). Similarly, cue-related activity in the striatum was lower in SCZ compared to HC. Secondly, a positive relationship was noted between the cue-period activity in LPFC and the level of intrinsic motivation in HC subjects was absent in SCZ patients (**Figure 2C**) (54). Thirdly, although the performance level per se was not significantly different between the two groups, the capacity of correction after error trials was somewhat different. To analyze it, we first distinguished the error trials into two types; "Undershoot" stands for the error when the button press is too fast (<4.95 s) while "Overshoot" stands for the error when the button press is too slow (>5.05 s). For example, in the trial after Overshoot, participants were required to regulate button press speed so as not to press the button too soon for success. As a result, the Success and Undershoot rates following Overshoot showed a significant between-group difference (**Figure 2D**), whereas those following Undershoot were not different. These results suggest that the regulation of button press after Overshoot, which is considered as a form of cognitive control, is impaired in SCZ patients (54). In addition, a positive relationship between the cue-period activity in LPFC and the Success rate after Overshoot was observed in healthy control subjects, but not in SCZ patients (54).

The lack of relationship between intrinsic motivation and LPFC activity suggests that SCZ patients do not adequately regulate actions because of impaired prefrontal activity (54). This is also supported by the absence of associations between the capacity to regulate response and LPFC activities. These observations are consistent with previous findings about reward processing. Despite the argument that SCZ patients exhibit a hedonic response comparable to that of HC subjects (75–77), these patients elicit lower motivation to initiate and retain an action (40, 78). Our finding suggests a failure to mediate between prediction of reward and action in people with SCZ (79, 80). In addition, it is suggested that information processing related to reward expectation is processed in the striatum and PFC (81), and the LPFC is a central brain area for enhancing actions related to reward expectations (82, 83). The PFC and the striatum are closely linked via the frontostriatal loops (84–87). Previous studies indicated that the neural activity in the ventral striatum to the reward expectation was impaired in SCZ patients (88–90). Based on these findings, it appears that SCZ patients have difficulty generating adequate action control in response to reward because of LPFC impairment.

Taken together, SCZ patients show motivation disturbances due to a weakened link between the reward expectation and goal-directed behavior which is associated with altered functions of LPFC and the striatum. Of particular importance is the difficulty of SCZ patients to adequately regulate actions on the basis of intrinsic motivation because of impaired prefrontal activity. Whether the neural system related to intrinsic motivation is different from that of extrinsic motivation remains unclear, which requires further research. For the greater chance of the success for CRT treatments, it will be beneficial to further explore the biological basis of intrinsic motivation and develop the methods to detect its individual differences.

FUTURE DIRECTIONS

Based on neuroimaging data from our studies, we are interested in discovering the ways to restore reduced neural activities in the striatum and LPFC. This strategy may lead to enhancement of intrinsic motivation and improvement of social functioning in people receiving a psychosocial treatment such as CRT. On the other hand, it has been reported that neural activity in LPFC and performance on cognitive tasks with high demands are impaired in SCZ patients (20, 21). These findings suggest that decreased activity of LPFC contributes to the impairment of both cognition and intrinsic motivation, leading to the difficulty in effectively improving cognitive impairment and social functioning. In electroencephalogram studies, enhanced frontal gamma-band oscillations have been associated with better performance in healthy subjects, while both reduced and excessive gamma-band oscillations have been suggested in patients with SCZ (91–93). Interestingly, rTMS has been reported to reduce abnormal gamma oscillations in patients with SCZ, whereas it increases gamma activity in healthy subjects during a cognitive task, which may be related to homeostatic plasticity (94). As this finding suggests that impaired prefrontal function can be modified by neuromodulation, the combination of CRT and neuromodulation may be one of the options to enhance social functioning.

At present, we have no objective and feasible scales of intrinsic motivation. However, by focusing on neural activity in LPFC evaluated in our recent studies (54) we may be able to develop a biological tool that can be applied in the clinical field. Near-infrared spectroscopy (NIRS) can be one of such techniques. It is non-invasive and can be measured under a restraint-free environment, thus suitable for psychiatric patients. The validity of NIRS has been indicated by significant correlations between fMRI BOLD signals and NIRS oxygenated hemoglobin (oxy-Hb) concentrations in the frontal area (95, 96). Using multi-channel NIRS, Pu et al. (97) reported that an increase in oxy-Hb concentrations in DLPFC is positively correlated with the interest and motivation scores in the Social Adaptation Self-Evaluation Scale in healthy subjects. This finding suggests that the NIRS signal in LPFC may provide an objective scale of intrinsic motivation in SCZ.

Although intrinsic motivation is considerably important to alleviate cognitive impairment, it is not easy to enhance intrinsic motivation of SCZ patients. Some studies report that extrinsic motivation induced by monetary rewards is useful to enhance the effect of CRT. According to the SDT, autonomous types of extrinsic motivation may switch to intrinsic motivation through the practice of CRT. The assessment of the construct of motivation in terms of levels of autonomy may provide useful information to achieve the maximum effect of CRT on cognition in patients with schizophrenia.

CONCLUSIONS

We reviewed putative neural correlates of intrinsic motivation revealed by neuroimaging data. In spite of previous attempts, we

have not yet established objective tools to monitor the degree of intrinsic motivation in each patient, which requires further investigations. Moreover, the development of CRT incorporating enhancement of intrinsic motivation, as well as autonomous types of extrinsic motivation, may be important, depending on the tendency for intrinsic motivation. These efforts are likely to enhance cognitive and social functioning in patients with SCZ.

AUTHOR CONTRIBUTIONS

KT drafted the manuscript. All authors critically reviewed the manuscript and approved the final manuscript.

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REVIEW
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Pharmacological Augmentation of Psychosocial and Remediation Training Efforts in Schizophrenia

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Pharmacological approaches to cognitive enhancement have received considerable attention but have not had considerable success in improving their cognitive and functional targets. Other intervention strategies, such as cognitive remediation therapy (CRT), have been shown to enhance cognitive performance but have not been found to improve functional outcomes without additional psychosocial interventions. Recently, several studies have attempted to enhance the effects of CRT by adding pharmacological interventions to the CRT treatments. In addition, as CRT has been shown to synergistically improve the effects of psychosocial interventions, the combination of pharmacological therapies aimed at cognition and psychosocial interventions may itself provide a promising strategy for improving functional outcomes. This review and commentary examines the current state of interventions combining CRT and psychosocial treatments with pharmacological augmentation. Our focus is on the specific level of effect of the pharmacological intervention, which could be enhancing motivation, training efficiency, or the consolidation of therapeutic gains. Different pharmacological strategies (e.g., stimulants, plasticity-inducing agents, or attentional or alertness enhancers) may have the potential to lead to different types of gains when combined with CRT or psychosocial interventions. The relative potential of these different mechanisms for immediate and durable effects is considered.

Keywords: schizophrenia, cognition, disability, everyday functioning, pharmacological cognitive enhancement, combination therapy

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INTRODUCTION

Cognitive impairments are prominent in several neuropsychiatric conditions (1). These impairments are functionally relevant and persistent over time and are minimally related to treatments for the illness (2). These impairments have spurred multiple treatment efforts spanning pharmacological, psychosocial, psychotherapeutic, and rehabilitation-based treatments. The rehabilitation-based treatments have used both in-person and computer-delivered cognitive remediation therapy (CRT) interventions (3). Furthermore, it has been suggested recently that combined pharmacological and cognitive remediation approaches may have the most promise for improving cognitive impairments in severe mental illness generally, and in schizophrenia specifically (4). However, much less attention has been paid to the potential combination of pharmacological treatments with psychosocial interventions. Pharmacological interventions may have the potential to synergistically combine with learning-based psychosocial treatments, much like the combination of these treatments with CRT training.

Previous reviews have analyzed the outcomes of both CRT and pharmacological interventions in schizophrenia and have demonstrated that the former is the more successful of the two. Clearly, cognitive remediation studies have demonstrated greater success, with several different studies finding effect sizes in the moderate to large range (3). In contrast, only a few studies have shown benefit for pharmacological treatments (5) and there is a lack of successful replication of these data and, to date, no positive phase III results have not been confirmed with larger samples in phase III studies (6). Thus, current research with pharmacological interventions have not demonstrated convincing ability to improve cognition as a monotherapy approach.

As the overarching goal of cognition-enhancing treatments is disability reduction, additional treatment approaches are needed to help achieve this. There have been multiple attempts to combine psychosocial interventions with CRT in order to enhance rehabilitation outcomes, but relatively fewer attempts to use the potential parallel strategy of combining targeted cognition-enhancing pharmacological therapies with psychosocial interventions. Most psychopharmacological and disability-targeted treatment data concern the pharmacological factors affecting interfere with the results of psychosocial interventions; however, this review focuses on the possibilities of additional therapeutic intervention.

In this article, we will focus on the combination interventions that could enhance cognitive performance and everyday functioning in people with schizophrenia. Encouraged by several very recent studies, we will examine the characteristics of CRT approaches that are suitable for combination with pharmacological interventions, as well as evaluating pharmacological interventions for their potential for combination with CRT, evaluating a model previously referred to as Pharmacologically Augmented Cognitive Training (PACT) (7). In addition to reviewing the possible benefits of combined CRT and pharmacological interventions, we also consider the possibility that combined pharmacological and psychosocial or psychotherapeutic interventions will have additional benefits when compared to either medication or behavioral intervention alone. The rationale for combining pharmacological cognitive enhancement with a psychosocial intervention is similar to that for adding CRT to a psychosocial intervention: using a synergistic therapeutic approach to enhance cognition through multiple strategies may enhance skill learning.

The evaluation of pharmacological strategies focuses on the mechanism of action, duration of effect, and potential impact on learning-based interventions such as cognitive remediation or behavioral interventions. This evaluation also necessitates a task analysis of CRT interventions, in terms of which cognitive processes are potentially important at different stages of the CRT participation process. Furthermore, available pharmacological interventions may interact with different stages of the CRT engagement process, which will refer to as performance-side variables.

An additional consideration when evaluating pharmacological augmentation of CRT is the fact that some augmentations may also increase the efficacy of CRT. For instance, if the rate of efficiency of training and gains across CRT levels was increased, it might also be the case that near transfer to neuropsychological test performance would be increased as well. There are several different ways that this increase could happen, including increased neuroplasticity (8) which could lead to greater beneficial brain changes with similar levels of effort and achievement.

FACTORS INFLUENCING THE EFFICACY OF CRT: PERFORMANCE-SIDE VARIABLES

Cognitive remediation therapy has been shown in multiple studies to improve performance on neuropsychological tests, although the efficacy of interventions varies across individuals (9). Several predictive factors for response to CRT have been identified, some of which may also be amenable to benefits from pharmacological interventions, as evaluated below.

There are several factors that can impact on the ability to perform in the training setting, and any of these factors can also influence gains during training. CRT differs from purely pharmacological interventions in that sustained effort-related participation on the part of the trainee is required. This level of effort is sustained for a training session that spans ≥30 min and thus, willingness and ability on the part of the trainee to participate in the training procedure is a prerequisite for training-related gains. While adherence to medication is clearly a participatory activity, the amount of effort expended, particularly in clinical treatment studies where medication is prepacked and delivered to the participant, seems less than that required to train for ≥30 min on a cognitively demanding task, ≥2 times/week.

MOTIVATION

Motivation has been shown to exert an influence on cognitive changes associated with CRT (10). There are different types of motivation, including motivation induced or maintained by extrinsic factors and motivation arising from intangible and self-generated factors, which is often referred to as "intrinsic" motivation. For instance, several studies by Medalia et al. have documented a positive relationship between intrinsic motivation and CRT outcomes (10–13). Intrinsic motivation refers to the willingness to perform the task because of the perception of benefit, rather than external rewards. The perception of intrinsic benefits is often augmented by certain elements of the CRT training process, such as bridging and discussion groups. It has been hypothesized that provision of external rewards for participating in CRT, such as financial compensation for training sessions, may lead to reduced transfer to other outcomes; however, it has recently been shown in a large-scale study that financial incentives to engage in behavioral rehabilitation programs do not lead to increases in clinician-rated engagement in treatment (14). In this study, individuals who showed high levels of motivation prior to treatment engagement demonstrated the greatest gains, while less motivated individuals did not show increased motivation, even with a potential to obtain considerable financial gain for increased treatment engagement.

Components of Motivation

Global Motivation to Participate in Therapeutic Activities

There are both global and specific components of motivation. Global motivation is the willingness to engage in an activity with

the expectation that some benefit will be received. Thus, global motivation may require the ability to understand the means-ends relationships between engagement in remediation interventions and possible real-world gains. Individuals who are unaware that they have either cognitive or everyday functional deficits could therefore be expected to be less likely to be motivated to engage in treatment.

In several previous studies, it has been shown that individuals with schizophrenia who are unaware of their clinical symptoms, or functional or cognitive limitations, are also most likely to report that they have high quality of life and no mood symptoms. For instance, in the large-scale CATIE study, patients who reported that they were "pleased" or "delighted" with their quality of life were rated clinically as having less awareness of their illness (15). Those same patients also reported minimal depressive symptoms, but performed more poorly on tests of executive functioning than patients who had less positive self-assessment of their quality of life.

A recent study has shown the connection between insight and cognitive performance in patients with schizophrenia, as well as improvements in their cognitive performance with treatment. In this study, clinically unstable patients with schizophrenia were recruited as inpatients and treated with lurasidone, quetiapine, or placebo (16, 17). The outcomes measured included ratings of their clinical symptoms as well as performance-based assessments of cognition. At baseline, approximately 33% of patients had performance-based cognition scores that were invalid, presumably because of lack of adequate engagement or effort made in the assessment process. Interestingly, clinical ratings of poor insight into illness were more severe in patients whose test performance was invalid. After antipsychotic treatment, clinical insight improved, and there was a statistically significant improvement in cognitive performance in the trial which was found to be correlated with improvements in insight. Furthermore, patients who provided invalid test performance at baseline were able to generate valid scores after pharmacological treatment.

These data suggest that lack of awareness of impairment may be associated with the inability or unwillingness to engage in cognitive testing. CRT is considerably more demanding than a one-time cognitive assessment, and thus unawareness of impairment clearly has the potential to reduce global motivation to engage in a therapeutic activity. Although there is little research on this topic, these findings also suggest that clinical stability, including the presence of the awareness of clinical, cognitive, and functional status may be a prerequisite for success CRT. As a result, one pharmacological intervention strategy to combine with CRT may be the administration of adequate levels of antipsychotic medications in order to maintain clinical stability and thus potentially augment CRT results.

Specific Components of Motivation to Engage in Computerized Training

Cognitive remediation therapy also requires the willingness to interact repeatedly with technology, either in the form of computers or tablet devices. One of the reasons for the success of contemporary CRT interventions is the continuous feedback delivered to the trainee. As most CRT interventions use titrated difficulty, the feedback is positive about 80% of the time on a trial by trial basis. Furthermore, most programs also deliver prizes, messages, and other tokens of achievement, with the goal of feedback being to have the participant find the experience rewarding, hence increasing their level of engagement and motivation to continue to participate. Receipt of tokens and other awards can be considered an extrinsic reward; however, performance feedback also aims to increase the intrinsic motivation to continue to improve in performance.

A further form of encouragement is offered in the form of in-person activities associated with many CRT programs. These activities often take the form of bridging groups, which are meetings designed to make the CRT experience meaningful and useful in real-world cognitively demanding situations. These interventions further aim to offer social support for engagement in a largely technology-oriented intervention. The inclusion of these groups has been argued to be necessary for successful gains in CRT treatment (18). However, it may be the case that, in order to achieve real-world functional gains, the additional intervention needs to be highly relevant to everyday functionality and targeted at those skills. At least two recent studies have shown that CRT combined with bridging groups did not improve performance on either everyday outcomes or on measures of the acquisition of everyday functional skills (19, 20). In one of them (19), CRT plus bridging improved cognitive performance, but not functional capacity or everyday outcomes, whereas CRT plus bridging plus functional skills training improved cognitive performance, functional capacity, and everyday outcomes (20).

There are some illness-specific challenges in schizophrenia, for example, deficits in sensitivity to rewards, both extrinsic and intrinsic, are commonly reported in patients with schizophrenia and may underlie some of the "anhedonic" features of the condition (21). Deficits in social motivation, including active social avoidance, are also common in schizophrenia (22). These motivational deficits have been shown to be more closely tied to social outcomes than neurocognition, social cognition, or even social competence (23–25). Thus, people with schizophrenia may not be sufficiently sensitive to rewards as unaffected individuals, and their social amotivation may also decrease their interest in bridging groups. In terms of extrinsic reward, it has been shown in several recent studies, reviewed by Gold et al. (26), that patients with schizophrenia are less responsive to financial reward for performing tasks than healthy comparison individuals, suggesting that reduced reward sensitivity applies to both tangible and intangible (i.e., social) reward systems.

It has been reported that self-administered CRT training has adherence rates of approximately 70% in both first episode psychosis, and the prodromal phases of the schizophrenia (27, 28). In these two studies, near transfer cognitive gains also appeared to be similar to previous studies that used in-person delivery of CRT, but not formal psychosocial interventions. Assessments to determine whether an individual with schizophrenia has high enough levels of active social avoidance to make coming in for treatment challenging may therefore be appropriate.

WHAT IS THE MECHANISM OF PHARMACOLOGICAL AUGMENTATION OF CRT?

Pharmacological interventions have the potential to change motivation through modifying perceived reinforcement. For instance, stimulant medications such as amphetamine and related compounds (e.g., methylphenidate) have the potential to increase sensitivity to reward. As compounds that directly influence the dopamine-mediated reward system, they may increase the reward salience of CRT tokens and awards (29), as well as potentially increasing the sensitivity to treatment gains of an intrinsic nature. They may also increase intrinsic motivation through changing the salience of social interactions, but this is less well-studied than reward augmentation. These compounds also have the potential to improve attentional performance, which has the face-valid implication of increasing the ability to concentrate on training tasks. Further, processing speed may be augmented by these interventions, which can make it easier to make more rapid early gains and solidify motivation to perform.

PACT RESULTS WITH STIMULANT MEDICATIONS: IS ATTENTION AUGMENTED?

A very recent study has suggested that single-dose amphetamine treatment immediately prior to CRT training leads to increased gains in performance on the training test. Swerdlow et al. treated patients with schizophrenia with 10 mg of amphetamine or placebo in a double blind cross-over design (30). A test for auditory attention processing was administered around before and after 60 min of auditory training. Compared to placebo, these data suggested that amphetamine treatment had a substantial benefit on gains during auditory training, suggesting that session by session administration of cognition-enhancing compounds can lead to greater attentional gains with CRT. Furthermore, the benefit of treatment persisted one week after a single 1-h training session, an effect not seen with placebo.

However, this study does not address the other hypothesis mentioned above; that stimulant treatment may enhance the reward salience of CRT tokens and awards, which could lead to sustained motivation to engage in the task. Also, the motivation to engage in treatment due to perception of long-term gains might also be changed through interventions that increase potential sensitivity to the need to engage in productive activities such as work. This is clearly an important research topic and would require additional research efforts.

Other compounds related to stimulants have also been examined for their augmentation potential. Most commonly, modafinil, an alertness promoting agent, has been studied for both direct cognitive benefits and for augmentation of PACT. The results from modafinil studies have been complex, in that several single-dose studies have reported positive effects of treatment with modafinil as a monotherapy (31), while several multiple dose studies did not find similar efficacy. In a recent 10-session PACT study comparing a standard dose of 200 mg of modafinil to placebo, with the MATRICS consensus cognitive battery (MCCB) as the outcome measure, there was no augmentation effect on CRT (32). Both groups improved in performance, but the performance of the group receiving only CRT was not so substantial that it could have led to a ceiling effect that obscured the effects of modafinil augmentation.

It is of interest, therefore, whether the results of Swerdlow et al. (30), which examined a single dose of amphetamine vs. placebo, would result in the same lack of efficacy if a multiple dose strategy was employed. If the single-dose effect habituates over time, then this would not be an effective intervention. Similarly, no studies have yet examined the consequences of daily dosing with stimulant-like medications on response to CRT interventions. Clearly, this is an area where more research would be important, particularly in terms of the relative benefit of single-dose, multidose day of training, and daily dosing regimens.

OTHER PHARMACOLOGICAL AUGMENTATION STRATEGIES

Cognitive remediation therapy has often been described as an intervention which promotes neuroplasticity. Changes in both brain structure and function are commonly noted after CRT interventions, with changes in white matter structure and cognitive activation in response to cognitive stimuli (33). In addition, changes in serum levels of brain-derived neurotrophic factor (BDNF) have been detected following CRT interventions (34). These changes approach full normalization of BDNF in cases treated with active CRT, while cases who participated in video game control treatment did not show these changes, despite equivalent levels of cognitive activity during the treatment period.

Pharmacological compounds too have the potential to lead to changes consistent with neuroplasticity. Compounds affecting the glutamatergic system have been cited as increasing brain plasticity response to various cognitive interventions in animal models (35). These interventions include increases in the rate of learning new information and the extent to which new information is rapidly consolidated in an adaptive manner. Much of this research has focused on facilitation of novel object recognition and maze learning paradigms (36). Both of these processes are also affected by antagonists at glutamatergic sites, including PCP and ketamine (37).

Importantly for this review, glutamatergic agents have been studied extensively in humans in other conditions because of their potential for modifying the learning process. In particular, D-cycloserine (DCS), initially used to consolidate fear extinction gains (38), has been studied for its potential to modify the memory consolidation process (39). This process is hypothesized to occur as a result of partial agonistic effects of DCS on *N*-methyl-D-aspartate glutamatergic receptors. This area of investigation has been challenging because, as DCS causes memory consolidation, it can cause consolidation of both the extinction of the older memories and consolidation of memory recurrence as well (40). Thus, DCS seems at present to have a

role in exposure interventions, but the treatment needs to be carefully administered.

There have been multiple studies of the direct effects of various glutamatergic agents on cognition. These results have been consistently negative when using DCS, cycloserine, glycine, and glycine transport inhibitors to improve cognition directly (41, 42). However, this does not mean that these compounds would not have a beneficial effect when combined with CRT interventions.

To date, there has been one study that used DCS in concert with CRT (43), which treated patients with schizophrenia with 50 mg of DCS vs. placebo once weekly, 60 min prior to receiving a CRT session. There was a target of 3 CRT sessions per week over a planned 8-week trial and participants completed an average of 26 training sessions. The results of the trial indicated that participants who were treated with DCS showed improvement on the tasks in the CRT training procedure, but not on external cognitive outcomes, as measured by MCCB, which improved in the placebo group but not the active treatment group. Furthermore, DCS improved negative symptoms in patients who had clinically significant symptoms of this type at baseline, although there was no connection between cognitive gains and negative symptom improvements. Thus, the results of this study are complex; DCS appeared to enhance performance on the training tests, but the fact that patients treated with placebo had greater near transfer of training to cognitive test performance suggests that DCS may interfere with the commonly found transfer of CRT gains to cognitive performance. While improving negative symptoms is an important goal of treatment, this study suggests that improving motivation-related symptoms does not necessarily lead to better ability to engage in cognitive training procedures. The interference with transfer to untrained tests also suggests that DCS may not be the optimal strategy to promote transfer, in terms of both near transfer to cognitive test performance, and far transfer to real world functioning.

An additional study examined the effects of a related pharmacological compound, d-serine, on augmentation of CRT in schizophrenia (44). In this study, it was found that augmentation of CRT treatment did not lead to incremental benefits. However, the authors reported good safety outcomes and suggested that a higher dose may be required.

CONCLUSION ON PACT

Pharmacological augmentation of CRT has been attempted and some success has been reported for certain study designs, primarily those using stimulant-like drugs. However, daily dosing studies have not yet been published yet, and studies of interventions aimed at increasing the potential neuroplasticity effect of CRT have been less successful to date. Furthermore, all of the possible dosing strategies and augmentation possibilities have not been explored. At this interim stage of the research process, the reasonable conclusion is therefore that this is a developing research area and more studies will most likely be reported in the immediate future which will hopefully enable firmer conclusions to be drawn.

PSYCHOSOCIAL REHABILITATION AND THE INTERFACE WITH COGNITIVE ENHANCEMENT

Psychosocial rehabilitation efforts can be targeted at multiple domains of disability. The two main areas of focus in the past have been social skills (often referred to as social competence) and vocational outcomes, which have both reported some success with psychosocial rehabilitation. For instance, supported employment programs using an individualized placement and support (IPS) model have found that participants who received high quality services had a rate of obtaining competitive employment of approximately 40%, compared to 10–15% for patients who received standard psychiatric rehabilitation services (45). For social skills training, a Cochrane systematic review suggested that average intervention was not more effective than discussion groups for improving social functioning, relapse rates, mental state or quality of life (46). As social cognition is a critical component of social outcomes, there have been multiple attempts to train social skills. These interventions have had several forms, including training focused on social interactions [Social Cognition Intervention Training (SCIT)] and computerized training interventions. Results of studies of SCIT have suggested that there is some moderate benefit on performance-based measures of social cognition, particularly measures of hostile interpersonal interactions, but minimal effects on real-world social outcomes (47–50). Computerized interventions have also shown some promise in terms of improving performance on social cognition measures. For instance, training on the Mind Reading: An Interactive Guide to Emotions (MRIGE) program improved social cognitive performance in individuals with an autism spectrum condition (51).

However, it is clear from the results of psychosocial interventions aimed at social functioning and vocational outcomes that, at most, half of the patients treated show benefit. Interestingly, it has also been shown that when compared to psychosocial interventions alone, patients who receive combined cognitive remediation and psychosocial interventions make more substantial and rapid gains. For instance, McGurk et al. (52) added approximately 20 sessions of CRT to an IPS model vocational intervention and found employment gains that were persistent for 3 years. In a follow-up study, McGurk et al. (53) also found that adding CRT to IPS in IPS non-responders led to a rapid and sustained improvement in employment outcomes, this demonstrating that augmenting cognitive functioning can lead improve the response to ongoing psychosocial intervention.

This CRT enhancement effect appears robust across various psychosocial interventions. Bowie et al. (20) compared monotherapy with skills training using the Functional Adaptation Skills Training (FAST) model developed by Patterson et al. (54) or CRT alone to a combined FAST and CRT intervention, finding that the combined group had significantly greater gains in everyday functioning outcomes than both other treatments, as rated by blinded observers. FAST or CRT as a monotherapy led to domain-specific gains (functional skills and cognition, respectively) but no psychosocial improvements. These results

suggest that CRT interventions can successfully combine with skills training interventions that are broadly aimed at functional skills in social, residential, and vocational domains.

Finally, Lindenmayer et al. (55) examined the combination of computerized social cognition training (MRIGE) and CRT compared with CRT alone on changes in performance-based assessments of social cognition and clinician ratings of clinical symptoms and social outcomes in patients with schizophrenia. Their study did not include a monotherapy social cognition arm, as their interest was in whether CRT improved social cognition. Their results indicated that the combined therapy lead to greater gains in performance on social cognitive tests as well as more gains in everyday social functioning without having a symptomatic benefit. Combining MRIGE and CRT did not dilute the effects of CRT on composite cognitive performance, which was significantly improved from baseline in both groups.

COGNITIVE BEHAVIOR THERAPY (CBT) AS AN AUGMENTATION TARGET

Another domain of psychosocial interventions aimed at improving symptoms of schizophrenia is that of CBT. CBT interventions are commonly targeted at treatment-refractory delusions or hallucinations. By their definition, CBT interventions require cognitive capacity for efficacy, and as a result, the substantial cognitive impairments seen in schizophrenia, even more salient in patients with evidence of clinical treatment resistance that would lead to CBT intervention, would seem to mitigate against the benefits of a learning-based therapy in patients with major learning problems. In fact, despite evidence of efficacy and considerable enthusiasm for CBT on the part of many proponents, the number needed to treat is higher than that for many pharmacological interventions (56).

Given that CBT interventions are targeted at populations selected for treatment-resistance and increased cognitive impairments, augmentation with CRT aimed at cognition would seem a viable strategy. Interestingly, there seems to be only one published study where CRT was combined with CBT in patients with severe mental illness (57). In that study, patients randomized to CRT prior to treatment with CBT had a more rapid response to CBT than cases randomized to other psychosocial interventions. A similar strategy could also be employed with pharmacological interventions. It would be straightforward to perform a randomized trial combining potential cognition-enhancing medications with CBT in order to see whether there was either faster response or increased benefit.

AUGMENTATION OF PSYCHOSOCIAL TRAINING WITH PHARMACOLOGICAL INTERVENTIONS

The substantial successes recorded from the combination of CRT and psychosocial interventions raise the question as to whether pharmacological augmentation strategies could lead to similar gains. While most pharmacological strategies have not had success on their own in terms of enhancement of cognitive performance, the combination of pharmacological interventions with CRT described above has led to incremental gains in some studies. Psychosocial interventions are themselves cognitively active and the possibility exists that synergistic effects could be seen with the combination of pharmacological augmentation of psychosocial interventions.

One interesting study has suggested that pharmacological factors may be critical for skills training interventions (58). It has been known for years that anticholinergic treatment of patients with schizophrenia is correlated with memory impairments. Memory impairments are functionally relevant, being one of the impairments most strongly correlated with everyday functional deficits. Even more important is the finding that anticholinergic medication levels correlate with the efficacy of CRT interventions. Specifically, Vinogradov et al. reported that serum levels of anticholinergic medications shared 20% of the variance with improvements in cognitive performance associated with CRT training. Thus, higher levels of anticholinergic medication can lead to more than just cross-sectional cognitive impairments, they can actually constrain the extent to which CRT provides a beneficial effect.

In another, recent study, similar effects were found for the influence of anticholinergic treatment and psychosocial treatments. Seventy patients with schizophrenia enrolled in psychosocial interventions were followed for 3 years (59). Total anticholinergic burden was assessed and patients were examined for cognitive performance and for progress in their psychosocial intervention programs. Anticholinergic burden predicted cognitive performance on the MCCB, which in turn predicted progress in rehabilitation. Clinical symptoms, antipsychotic treatments, and baseline level of functioning did not add variance to the MCCB scores for prediction of rehabilitation outcome. These data provide convincing evidence for the direct adverse effects on skills training of anticholinergic medications.

PROCHOLINERGIC TREATMENTS FOR AUGMENTATION OF SKILLS TRAINING

Directly in line with the idea that that the cholinergic system may be critical for successful CRT and psychosocial intervention is the idea that procholinergic treatments may be a reasonable pharmacological enhancement strategy. There are two different approaches to procholinergic treatment: treatment with compounds that affect the muscarinic cholinergic system and others that target the nicotinic cholinergic system. Muscarinic targets have included M1 agonists and, much more commonly, acetylcholinesterase inhibitors (AChEIs). Nictonic targets have included a variety of partial agonist strategies aimed at the α-7 receptor with a smaller number of studies targeting a different receptor complex the α4β2.

Results from studies of the direct effect of cognitive enhancement with AChEI have been consistent and disappointing. Three different AChEI (donepezil, galantamine, and rivastigmine) have shown preliminary success in small scale studies, but larger studies have been consistently negative (60–62). In fact, in one study, placebo treatment was superior to active treatment with

donepezil (62). Another large-scale study examining galantamine (61) showed some that there were some domains of cognition that were potentially beneficially affected, but the overall effects of treatment on the predetermined cognitive outcomes were negative.

There have been other studies in patient with schizophrenia using the M1 agonist xanomeline (63). Although the compound appears to have efficacy for cognitive performance, its original manufacturer stopped its development because of significant gastrointestinal distress which lead to a substantial rate of discontinuation. At the present time, there are efforts to bypass the toxic effects of M1 agonist compounds by attempting to deactivate the mechanisms responsible for some of the side effects of the treatment.

Results with α4β2 treatments have also been reported. In a substantially powered randomized trial, the α4β2 compound varenicline was found to work as an effective smoking-cessation treatment, but did not have any detectable cognitive benefits, as measured by MCCB (64).

There has been much a more substantial effort in the domain of α-7 receptor agonists; however, results have been inconsistent. Several different treatments have failed to show differences from placebo in studies on patients with schizophrenia (65, 66). A short-term study of the α-7 receptor agonist DMXB-A found separation between active and placebo treatment in a cross-over design (67). However, a longer study with more participants found no beneficial effects of treatment (68). There were reports of substantial successes in a phase II clinical trial, which also had suitable coprimary measures (69). However, this drug also failed to separate from placebo in a much larger-scale phase III study of patients with schizophrenia (Hilts et al., in preparation). Finally, in a much smaller study, the mixed α-7/α4β2 receptor agonist tropisetron was reported to improve cognition in three different samples of 10 patients with schizophrenia compared with placebo (70). However, given the repeated failures of larger studies in this research area to replicate the results of smaller studies and the fact that tropisetron has been in clinical use for two decades for smoking cessation, a much larger confirmatory study will be needed.

The failures of procholinergic agents as monotherapy for cognition in schizophrenia do not necessarily mean that they would not be effective in improving the efficacy of either CRT or psychosocial interventions. Indeed, there is a precedent for a specified combination of a pharmacological agent and a psychosocial intervention: varenicline as an adjunct to clinical interventions for smoking cessation. Although varenicline may lead to reduced smoking in some populations, it has not been approved as a monotherapy. Thus, it is entirely possible that a combination of a pharmacological agent not approved on its own and either a CRT or psychosocial intervention could happen in the future.

Testing such interventions would seem to be a priority but may be challenging while funding agencies insist that all interventions targeted at severe mental illness have an identifiable, separable, and discretely measurable target to engage. In fact, the most recent developments in the "precision medicine" initiative of the National Institute of Mental Health (NIMH) have argued for an identifiable, single target and clear specifications of what constitutes a negative result. While neuropsychological tests can be easily specified as the targets for both pharmacological agents and CRT, the "target" for skills training may be more difficult to define. While Bowie et al. (20) used performance on a measure of functional capacity (the UPSA-B) as the index of treatment gains associated with a highly specific skills training program, vocational interventions are more challenging. While no one would argue that increases in hours worked or money earned is not important, it easy to criticize on the basis that there are multiple potential mechanisms of influence that could move these outcomes in a positive direction. Thus, the combination of pharmacological interventions with broader psychosocial interventions such as IPS is outside the realm of NIMH support at this time. A test of whether pharmacological mechanisms combined with IPS may therefore have to wait for the approval of a medication for cognitive impairment associated with schizophrenia and funding by the owner of the medication.

OTHER PHARMACOLOGICAL AUGMENTATION STRATEGIES

There have been several other domains of pharmacological interventions aimed at cognition in the schizophrenia spectrum, including interventions targeted at subclasses of monoamines, including dopamine D1 receptors and norepinephrine. D1 receptors have been an interesting target since animal work conducted by Patricia Goldman-Rakic et al. in the 1990s. Specifically, the D1 receptor agonist SKF 38393 was shown in several studies to have a direct beneficial effect on cognition in several animal models (71), although this compound does not cross the blood brain barrier in adequate concentrations to be useful for pharmacological augmentation. Other D1 agents, including dihydrexadine (DHX), have been tested in clinical trials. Although DHX did not lead to significant improvement in cognition in patients with schizophrenia (72), it was found to lead to significant improvements in working memory in patients with schizotypal personality disorder who had never been treated with antipsychotic medications (73). Broad spectrum dopamine agents such as pergolide (74) and pramipexole (75) have been examined in patients with schizotypal personality disorder and schizophrenia, respectively. However, pergolide has since been removed from the market because of adverse events, and pramipexole did not show remarkable efficacy in schizophrenia although it does not appear to have been tested in schizotypal personality disorder.

Similar findings were reported for the noradrenergic alpha-II agonist guanfacine, a currently approved treatment for attention deficit hyperactivity disorder found to improve cognition in animal models (76). In a clinical trial for schizophrenia, guanfacine did not improve cognition (77), but when used to treat patients with schizotypal personality disorder there was a significant positive treatment effect (78). Other noradrenergic interventions have also provided promising data, but have shown limited clinical efficacy in schizophrenia. For example, Friedman et al. (79) found that atomoxetine, a norepinephrine transport inhibitor, improved regional blood flow in critical

areas compared to placebo in patients with schizophrenia; however, the cognitive benefits of the treatment did not achieve statistical significance. Kelly et al. (80) performed a 32-patient randomized trial and also did not find separation from placebo. However, all of these interventions have been tested only as monotherapy, without additional CRT or psychosocial interventions. The fact that cognition did not improve with these treatments does not mean that they would not manifest an incremental efficacy boost to these other learning-based interventions. As all of these treatments have demonstrated safety and tolerability, studies of combined therapy with these pharmacological strategies and CRT or psychosocial interventions would be able to proceed without many concerns about safety.

CONCLUSION

Combining pharmacological interventions with CRT has been suggested as a promising way forward for improving cognition in schizophrenia and has been previously tested in randomized research trials. There are several different levels at which cognition-enhancing drugs could beneficially impact on the results of CRT, including making it easier for participants to engage in CRT (performance-side variables) as well as augmenting the extent to which these interventions have a benefit (increasing plasticity). Furthermore, a larger cognitive gain with combined therapy might also be more likely to lead to functional gains without the requirement for psychosocial interventions. Despite the substantial gains seen with some CRT interventions, including average effect sizes of $d = 0.8$, patients in those trials still have substantial cognitive deficits at the end of the study. If those effect sizes could be doubled, then cognitive performance could be normalized, which might have implications for whether additional skills training would necessarily be required.

The results of studies combining pharmacological and CRT interventions have been mixed, as a function of the mechanism of the pharmacological add-on strategy. It is possible that the research designs employed in unsuccessful studies were not optimal, such as those including single-dose treatments, medications that may actually impair learning or transfer of information, or concerns regarding the dosing of the CRT interventions delivered.

Much less mixed are the results of combining cognitive enhancement induced by CRT with psychosocial interventions. These studies have consistently found augmented rates of acquisition of psychosocial target outcomes in cases who received also CRT interventions. Finally, although in its infancy, another area where cognition-enhancing interventions could be explored is their potential ability to facilitate clinical gains in CBT, as per the single study that suggested CRT may lead to an incremental benefit for CBT. This would obviously be an area where a combined trial design could employ a pharmacological cognitive enhancer instead of CRT as a cognitive enhancement strategy to boost the efficacy of CBT.

We suggest that similar research strategies could also be employed with pharmacological augmentation, using a research design where a putative cognition-enhancing compound was added to psychosocial interventions in a randomized trial. There are currently limited data regarding this, but there are many promising agents to test. The pragmatics of pharmacological augmentation by-pass the effort and motivation-related limitations associated with some CRT interventions. This is a largely unexplored area, but the synergistic effect of psychosocial interventions and pharmacological treatment strategies seems worthy of exploration.

A final consideration is whether the triple combination of pharmacological, CRT, and psychosocial interventions would be superior to the results of combining CRT and psychosocial interventions alone. If pharmacological augmentation of CRT is actually beneficial and increases gains compared to CRT alone, then this combination might lead to even greater functional gains when combined with psychosocial interventions. This is, of course, a research question that can be addressed directly.

AUTHOR CONTRIBUTIONS

Both authors contributed equally to this article.

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Enhancing Neuroplasticity to Augment Cognitive Remediation in Schizophrenia

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There is a burgeoning need for innovative treatment strategies to improve the cognitive deficits in schizophrenia. Cognitive remediation (CR) is effective at the group level, but the variability in treatment response is large. Given that CR may depend on intact neuroplasticity to produce cognitive gains, it is reasonable to combine it with strategies that harness patients' neuroplastic potential. In this review, we discuss two non-pharmacological approaches that can enhance neuroplasticity and possibly augment the effects of CR in schizophrenia: physical exercise and transcranial direct current stimulation (tDCS). Substantial body of evidence supports the beneficial effect of physical exercise on cognition, and a handful of studies in schizophrenia have shown that physical exercise in conjunction with CR has a larger impact on cognition than CR alone. Physical exercise is thought to stimulate neuroplasticity through the regulation of central growth factors, and current evidence points to brain-derived neurotrophic factor as the potential underlying mechanism through which physical exercise might enhance the effectiveness of CR. tDCS has emerged as a potential tool for cognitive enhancement and seems to affect the cellular mechanisms involved in long-term potentiation (LTP). A few reports have demonstrated the feasibility of integrating tDCS with CR in schizophrenia, but there are insufficient data to determine if this multimodal approach leads to incremental performance gain in patients. Larger randomized controlled trials are necessary to understand the mechanisms of the combined tDCS–CR intervention. Future research should take advantage of new developments in neuroplasticity paradigms to examine the effects of these interventions on LTP.

Keywords: schizophrenia, cognitive training, remediation, physical exercise, transcranial direct current stimulation, neuromodulation, neuroplasticity, brain-derived neurotrophic factor

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INTRODUCTION

Antipsychotic medications are useful in ameliorating positive symptoms of schizophrenia, but they have little effect on cognitive deficits (1, 2). Efforts to improve cognitive deficits in schizophrenia are of paramount importance as they are among the strongest predictors of patients' functional outcome (3). Most of the efforts for cognition enhancement have used pharmacological approaches (i.e., drugs that enhance learning and memory in animal models) (4). However, the results in larger trials have

been disappointing, and currently, there is no drug approved for cognition enhancement in schizophrenia (5). Therefore, treatment studies in this population have started to shift to cognitive remediation (CR) strategies. Although CR in schizophrenia is effective at the group level (6, 7), there is substantial individual variability in treatment response, and many patients exhibit little benefit (8). Moreover, the training effects resulting from CR alone do not always generalize to improvements in real-life functioning (9). Thus, as the best validated treatment for the cognitive dysfunction in schizophrenia, CR only leads to a moderate effect-size improvement in cognition (0.45), with an even lower impact on daily functioning (0.36) (6, 9). It is, therefore, critical to consider ways of enhancing the impact of CR.

Recently, "neuroplasticity-based" interventions have been developed to train perceptual processes in schizophrenia, while also engaging attentional and working memory operations (10). These interventions are explicitly designed to drive adaptive plastic changes throughout distributed prefrontal–temporo–parietal systems (11). Many studies in schizophrenia patients have demonstrated that this neuroscience-informed approach to training generates meaningful restoration of prefrontal functions and higher-order cognition (12–14), with associated improvements in community functioning (15). Thus, neuroplasticity may be an important mechanism underlying effective intervention approaches. However, this CR method requires lengthy hours of repetitive, intensive practice to induce significant changes. Combining CR with strategies that promote neuroplasticity may not only lead to larger and longer-lasting improvements, but also require shorter training protocols. Although there have been efforts to combine CR with cognitive-enhancing medications that affect neuroplasticity, such as D-cycloserine (16) and modafinil (17), less attention has been devoted to non-pharmacological approaches that could potentially augment CR effects and maximize improvements in functional outcomes. In this brief review, we will discuss two recent non-pharmacological approaches that are thought to enhance neuroplasticity in schizophrenia: physical exercise and transcranial direct current stimulation (tDCS). It should be noted that there are many other neurostimulation techniques that have been discussed in the literature, such as transcranial magnetic stimulation (TMS), transcranial electrical stimulation (TES), magnetic seizure therapy, vagus nerve stimulation, and deep brain stimulation. However, only tDCS has been combined with CR.

REVIEW OF PHYSICAL EXERCISE AND tDCS STUDIES

Physical Exercise and Cognition

The beneficial effects of physical exercise on cognition are well documented in healthy individuals, as well as across many medical and psychiatric illnesses (18–20). Accumulating evidence suggests that exercise reduces pro-inflammatory processes and peripheral risk factors (i.e., obesity and diabetes) that are associated with cognitive decline (21). Furthermore, it stimulates hippocampal neuroplasticity and promotes angiogenesis, neurogenesis, and synaptogenesis through the regulation of central growth factors (22). The mechanisms of exercise-induced cognitive improvements seem, to a large extent, to be related to an increased production of brain-derived neurotrophic factor (BDNF), which plays a pivotal role in synaptic plasticity and is particularly important for learning and memory (18, 23, 24). Similar to CR (25), exercise (26) has been shown to increase peripheral BDNF levels.

As the two approaches could potentially enhance cognition through overlapping neurobiological mechanisms, adding exercise to a CR program may further harness patients' neuroplastic potential and lead to cognitive gains beyond that achieved by CR alone. The evidence from animal research suggests some benefit from combining these approaches. Fabel et al. (27), for example, showed that a combination of aerobic exercise and cognitive enrichment for rodents had beneficial effects on neurogenesis, leading to a 30% greater increase in new neurons than either activity alone. Several reports in healthy older adults have compared the separate vs. combined effects of CR and exercise and shown superior effects of the combined intervention on verbal/working memory (28, 29), divided attention (30), as well as global cognitive performance and everyday functioning (31). Studies in children (32) have also shown that training programs that integrate physical exercise with computer-based training games improved learning and increased gains on school-administered math and reading achievement tests.

Physical Exercise in Schizophrenia

Physical activity has been shown to ameliorate the psychotic and negative symptoms of schizophrenia and improve patients' quality of life by reducing health problems often associated with the illness (33, 34). Randomized controlled trials (RCTs) have been published recently demonstrating that physical exercise, especially aerobic exercise, improves cognitive functioning in schizophrenia patients, with corresponding increases in white matter integrity and structural connectivity (35), hippocampal volume (36), and BDNF signaling (37). A recent meta-analysis (38) identified 10 trials (7 RCTs and 3 non-randomized studies) evaluating the cognitive effects of exercise in schizophrenia. Pooled effect sizes across all outcomes showed that exercise significantly improved cognition (particularly attention, working memory, and social cognition) more than the control conditions. The treatment effect size of 0.33 (95% CI = 0.13–0.53, $p = 0.001$) across all studies and 0.43 (95% CI = 0.21–0.66, $p < 0.001$) in RCTs suggests that the beneficial effect of exercise on cognition in schizophrenia is comparable to that of CR.

Physical Exercise plus CR in Schizophrenia

We are aware of three published studies that have combined CR and exercise in schizophrenia. In one study (39), 29 patients were randomly assigned to either CR and exercise or CR and mental relaxation. The interventions were 4-week long and consisted of three weekly sessions (30 min of CR and 45 min of either aerobic exercise or relaxation). Both groups showed cognitive gains in the domains of processing speed, working memory, and visual learning, improvement in subjective well-being, and reduction

in negative symptoms. However, the effects were superior for the combined cognitive and physical training group.

In another study (40), 22 patients were enrolled in a 12-week endurance-training program augmented with CR and compared to a matched control group. Patients in the endurance training group exercised on bicycle ergometers, while those in the control group played table soccer for 30 min three times a week. After 6 weeks of the intervention period, CR was added in each group, for two 30 min-sessions a week. Results showed that, compared to the control condition, endurance training and CR significantly improved short- and long-term verbal memory, cognitive flexibility, global and social functioning, and negative symptoms. Unfortunately, the lack of random assignment, baseline differences between the groups, and the fact that the cognitive and clinical improvement in the combined training group was only seen after CR was added to the intervention make the findings difficult to interpret.

Last, a pilot study of recent-onset schizophrenia patients randomly assigned participants to 10 weeks of CR and exercise ($n = 7$) or CR alone ($n = 9$) (41). The CR intervention consisted of 2 h of auditory and social cognitive training twice/week, and exercise consisted of 30–45 min of aerobic conditioning 4 days/week. Results showed that the differential gains in global cognition and functional outcome were larger in the combined intervention group relative to the CR group, with Cohen's *f* effect sizes of 0.48 for the MCCB overall composite and 0.88 for independent living skills.

tDCS and Cognition

In recent years, neurostimulation has been developed as a non-invasive tool for cognitive enhancement (42, 43), with a primary advantage of having fewer side effects than pharmacological treatment (44). Unlike other brain stimulation techniques (e.g., TMS, TES), tDCS uses a weak electrical current (1–2 mA) to alter spontaneous neuronal network activity by shifting membrane potentials in a hyperpolarizing or depolarizing direction without inducing neuronal firing (45–47). tDCS changes the excitability of neurons in a polarity-dependent manner (48), such that anodal stimulation enhances cortical excitability, whereas cathodal stimulation decreases it (49). Various electrode montages can be applied to the scalp to modulate different areas of activity in the brain. Although tDCS has coarse spatial targeting, a few minutes of stimulation can lead to changes in cortical excitability lasting for over an hour (50).

The therapeutic effect of tDCS is thought to stem from its impact on the cellular and molecular mechanisms involved in long-term potentiation (LTP) (51, 52), and its after effects seem to be NMDA-receptor dependent (53). Thus, similar to physical exercise (21) and CR (54), tDCS appears to increase cortical plasticity (55) and could have additive or synergistic effects with CR, allowing for better cognitive outcomes.

A handful of studies in healthy samples have administered tDCS during specialized cognitive training and shown a performance-enhancing effect on the trained task (56) and generalization to untrained tasks (57). For instance, Martin et al. (56) demonstrated increased accuracy on a dual-working memory task during concurrent active tDCS vs. sham, but the effect was only present during the stimulation period and did not result in greater subsequent learning. This short-lived "online" effect has also been observed during combined tDCS and behavioral inhibition training (58). Additionally, Andrews et al. (57) found that completing an n-back task while receiving tDCS resulted in greater improvement in performance on Digit Span Forward compared to either tDCS or the cognitive activity alone. Similarly, the simultaneous administration of tDCS and computerized CR in healthy older adults significantly improved working memory compared with CR alone (59). The superiority in performance with this integrated approach was also evident in studies combining multiple repeated tDCS sessions with training on a motor skill task (52) and artificial numerical learning task (60).

tDCS in Schizophrenia

Most studies examining the effects of tDCS in schizophrenia have administered the stimulation at rest, while the subject is engaged in a passive activity, such as watching a movie, followed by an "offline" assessment of interest. In different randomized sham-controlled trials, tDCS was found to enhance working memory (61), probabilistic association learning (62), and composite scores on measures of cognition (63), when applied to the left dorsolateral prefrontal cortex. More specifically, Hoy et al. (61) reported significantly better performance over time on a working memory task following a single tDCS session compared to sham ($p = 0.027$). Although Vercammen et al. (62) found no significant effect at the group level, a subgroup of patients with adequate learning at baseline improved with active tDCS. In Smith et al.'s RCT (63), active compared to sham tDCS subjects showed significant improvements after the fifth tDCS session in the MCCB overall composite ($p = 0.008$) and the working memory ($p = 0.002$) and attention-vigilance ($p = 0.027$) domain scores, with large effect sizes (Cohen's *d* values ranged from 0.84 to 1.25). There is also evidence that tDCS can ameliorate auditory hallucinations (64, 65) and negative symptoms (66) in patients, as well as modulate the amplitude of the mismatch negativity, an EEG index of basic auditory processing (67).

tDCS plus CR in Schizophrenia

Schizophrenia researchers have recently begun to investigate the feasibility and efficacy of integrating tDCS and CR. There are currently four published reports in this area, mostly piloting this procedure in small clinical samples. In one study (68), two patients received a neuroplasticity-based CR intervention combined with tDCS and showed cognitive improvements that were maintained at 1-month follow-up. The 4-week intervention consisted of five 45-min auditory training sessions a week with active tDCS administered concurrently with CR on three sessions per week. In another pilot study (69), patients ($n = 10$) received three working memory training sessions a week for 16 weeks, with active or sham tDCS applied during two of the CR sessions each week starting in week 3. The authors reported enhanced cognitive performance on word and picture N-back tasks and MCCB overall composite when CR was paired with tDCS. In a negative findings study (70), 10 patients were randomized to either active or sham tDCS (10 consecutive sessions over 5 days), with cognitive training (administration of n-back and sequence

learning tasks) randomly applied during one of the tDCS sessions. The combined approach failed to improve clinical symptoms and cognitive performance.

In the largest study to date (71), investigators randomly assigned 49 patients to CR (training on a working memory and implicit learning task) and either active ($n = 24$) or sham tDCS ($n = 25$). The intervention was relatively short and consisted of four cognitive training days (day 1, day 2, day 14, and day 56), with two sessions on each day. tDCS was administered concomitantly with CR during the second session of days 1 and 14. Results showed significantly better working memory performance in the CR and active tDCS group relative to the CR and sham tDCS group. Surprisingly, the improved performance was evident on days 2 and 56, suggesting that tDCS had no enhancing effects during the acute stimulation but rather long-term effects on consolidation and learning.

CONCLUSION AND FUTURE DIRECTIONS

Based on the aforementioned review, it appears that both physical exercise and tDCS are intriguing candidates for augmenting the therapeutic effects of CR in schizophrenia. Current evidence suggests that a multimodal intervention that combines CR with physical exercise has a larger impact on cognitive functioning than CR alone. Moreover, there is strong evidence implicating BDNF as the mechanism underlying the cognitive-physical training approach (30, 41). Nonetheless, despite the promise that exercise has shown in augmenting CR in schizophrenia, there are several methodological issues that remain unresolved. For example, the literature is not consistent regarding the type, frequency, intensity, and duration of physical training necessary to produce the beneficial effects. Aerobic exercise has been the most studied and has produced the most consistent effects on cognition. However, other types of physical activity, such as yoga (72, 73), high-intensity interval training (74), and high-velocity circuit resistance training (75) deserve further attention. Furthermore, although Firth et al. (38) showed that a greater amount of exercise is associated with larger cognitive improvement, Kimhy et al. (76) found that it is the fidelity with target training intensity, rather than the frequency and duration of exercise, which correlates with changes in cognition. Some review studies (23, 72, 77) suggest a minimum of three sessions per week (at least 30 min/session) of moderate-intensity aerobic training for schizophrenia patients, administered in a supervised group setting for a minimum of 12 weeks, which is in line with recommendations by the American College of Sports Medicine (78).

In addition to refining optimal exercise training parameters, it is also essential to consider the timing of exercise with respect to CR when combining the two approaches. For instance, it might be more beneficial to start a treatment session with aerobic exercise followed by CR, as some studies have shown that engaging in physical activity before or while performing a cognitively demanding task improves learning or performance on the task (40). In a recent review (79), the authors proposed that aerobic exercise preceding CR may create a state of neuroplastic readiness in the brain through BDNF upregulation, which can potentiate the effectiveness of CR.

As far as the concurrent administration of tDCS and CR, emerging data support the feasibility and tolerability of this approach, but additional studies are needed to determine if it leads to performance gain in schizophrenia patients. Although the duration of stimulation of around 20 min has been consistently employed across studies, the therapeutic dose (i.e., number of sessions per day or week) has yet to be established. A host of parameters may moderate the effects of tDCS on cognitive outcomes, including placement and size of anodal/cathodal electrodes, unilateral vs. bilateral stimulation, amplitude of stimulation, and selection of training tasks during stimulation. Although it has been suggested that neuromodulation in combination with memory training may enhance the effects of training *via* LTP (80), the underlying mechanisms of tDCS have been mainly explored within the motor cortex and not memory-related regions. Therefore, beyond methodological research to identify a standard montage and the parameters required for therapeutic tDCS administration, larger RCTs are necessary to establish efficacy and relevant mechanisms of the combined tDCS–CR intervention.

Both approaches seem to have the potential to enhance the impact of CR by affecting functions that underlie neuroplasticity (55, 81). Fortunately, it is now possible to measure neuroplasticity *in vivo* in humans using neuroimaging techniques (e.g., EEG and fMRI). New paradigms have been recently developed to assess LTP non-invasively using repetitive sensory stimulation. Similar to electrical stimulation in animals (82), repetitive high-frequency stimulation (HFS) can induce LTP-like effects in humans (83–87). Some studies have measured LTP-like plasticity using a paradigm in which visual-evoked potentials (VEPs) to visual stimuli are recorded before and after the same stimulus is presented at a high frequency. Enhancement (increase in amplitude) of the VEPs after HFS is thought to reflect experience-dependent neuroplasticity of the visual cortex (84, 86–88). So far, two studies have been published using this EEG paradigm in schizophrenia (88, 89). Future treatment studies in schizophrenia should take advantage of these novel, non-invasive methods of assessing neuroplasticity to directly test whether physical exercise or tDCS affect LTP. For example, we are currently conducting an RCT in which a visual LTP paradigm is an outcome measure to examine changes in neuroplasticity following cognitive training.

In the absence of any robust pharmacological treatments for cognitive deficits in schizophrenia, physical exercise and tDCS are feasible and intriguing adjunctive treatments to enhance neuroplasticity and augment the effects of CR. While showing promise, their efficacy still needs to be demonstrated in more rigorously controlled studies.

AUTHOR CONTRIBUTIONS

CJ performed the literature search and drafted the manuscript. YR and MG critically reviewed the manuscript. All the authors read and approved the final manuscript.

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Possible Facilitative Effects of Repeated Anodal Transcranial Direct Current Stimulation on Functional Outcome 1 Month Later in Schizophrenia: An Open Trial

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Recent research on neuromodulation techniques, such as transcranial direct current stimulation (tDCS), for the treatment of schizophrenia has mainly focused on psychotic symptoms. We aimed to determine whether repetitive tDCS is efficacious in improving determinants of outcome, such as cognitive function, daily living skills, and depressive mood in patients with schizophrenia. Twenty-eight patients underwent tDCS (2 mA × 20 min) two times per day for 5 consecutive days. The anodal electrode was placed over the left dorsolateral prefrontal cortex while the cathodal electrode was placed over the right supraorbital region. One month after the last stimulation, there was a significant improvement on cognitive function, measured by the brief assessment of cognition in schizophrenia ($d = 0.49$). Significant effects were also shown on daily living skills (functional capacity), measured by the UCSD performance-based skills assessment-brief ($d = 0.70$). Depressive symptoms, measured by the Calgary depression rating scale, as well as psychotic symptoms measured by on the positive and negative syndrome scale positive and general psychopathology subscales also responded to the treatment ($d = 0.38$, $d = 0.48$, and $d = 0.50$, respectively). This is the first study to suggest that tDCS with the anodal electrode on the left prefrontal cortex improves functional capacity and depressive symptoms in patients with schizophrenia. These results may add to the concept that tDCS provides a strategy to enhance functional outcomes in patients with schizophrenia.

Trial Registration: https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000018556, UMIN000015953.

Keywords: brain stimulation, cognition, daily living skills, tDCS, functional outcome

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INTRODUCTION

Schizophrenia patients elicit psychotic symptoms, mood symptoms, and cognitive impairment (1–3). Specifically, cognitive function, such as learning memory, working memory, executive function, verbal fluency, and attention/information processing, are impaired in patients with the illness (4, 5). Functional capacity is defined as the potential to perform everyday living activities, which require financial competence, communication skills, and so on (6). By contrast, real-world functional outcomes (social function) are greatly affected by several factors, such as opportunities and incentives

that influence functioning in everyday situations (7). These levels of functional outcomes (cognitive function, functional capacity, social function) have been reported to be associated with each other (8, 9).

In patients with schizophrenia, functional connectivity of the frontoparietal control network and inter-hemispheric connectivity are decreased, which may play an important role in the pathophysiology of impairment of higher order cognitive task-related activities (10–12). The dorsolateral prefrontal cortex (DLPFC) is reported to be related to these circuits, and shows functional changes of cognitive function in schizophrenia (13, 14). Transcranial direct current stimulation (tDCS) is a feasible and safe method, using weak and direct electrical current to the brain through electrodes (15, 16). tDCS changes cortical excitability, modulated by glutamatergic activity *via* actions on catecholamine, acetylcholine and serotonin receptors (17–19). With this mechanism, tDCS over the left DLPFC has been suggested to modulate corticosubcortical/corticocortical pathways (20, 21).

The beneficial effect of tDCS on cognitive function has been reported. For example, Vercammen et al. observed that a subset of patients with schizophrenia, with greater variance in the active relative to the sham conditions, may respond to tDCS over the DLPFC (22). In addition, Schretlen et al. reported facilitative effects of tDCS over the left DLPFC on measures of working memory and aspects of verbal fluency relevant to word retrieval (18). Moreover, Hoy et al. found that repeated tDCS over the left DLPFC may enhance working memory in schizophrenia by restoring normal gamma oscillatory function (23). Furthermore, a sham-controlled randomized study demonstrated that repeated tDCS over the left DLPFC improved performance on the MATRICS Consensus Cognitive Battery (24). Thus, the DLPFC has been a target for studies investigating tDCS on cognitive function in schizophrenia (18, 22–24).

Although these studies indicate the facilitative effect of tDCS over the DLPFC on some domains of cognitive function, there is little information on whether tDCS would improve a higher level of functional outcome, e.g., daily living skill linked to cognitive function (functional capacity), in schizophrenia. We hypothesized that tDCS may also be effective in improving functional capacity in schizophrenia, since this level of functional outcome is associated with cognitive function, as mentioned above (8, 9). To our knowledge, no study has been attempted to determine whether tDCS directly improves functional capacity, or the improvement on other symptoms, such as psychosis, depression, would indirectly improves it. Based on these considerations, the primary aim of present study was to evaluate the effect of anodal tDCS over the left DLPFC on functional capacity in schizophrenia. Also, we sought to determine whether or not a putative improvement of functional capacity by tDCS would be related to changes of other clinical factors, such as cognition, psychotic symptoms, and depressive symptoms.

MATERIALS AND METHODS

Participants

Inpatients or outpatients treated at National Center Hospital, National Center of Neurology and Psychiatry, were enrolled. Participants were recruited by psychiatrists' referrals. They provided written informed consent before starting the trial.

Subjects met the following inclusion criteria:

(1) Meeting DSM-5 criteria for schizophrenia.
(2) Being 20 through 60 years old.
(3) Being able to sign and give consent.

Patients with any of the following diagnoses in accordance with clinical interview by psychiatrists were excluded from the study:

(1) Alcohol or substance disorder
(2) Traumatic brain injury
(3) Epilepsy

Twenty-eight subjects were enrolled, and completed the study without any dropout. Baseline characteristics of patients are shown in **Table 1**. The mean and standard deviation of premorbid IQ assessed by the Japanese Adult Reading Test (25) was 99.6 (12.0). The mean standard deviation of the global assessment of functioning (26) was 38.6 (6.9). Antipsychotics taken by participants were as follows: risperidone (eight patients), paliperidone, quetiapine, aripiprazole (seven for each), olanzapine (six), haloperidol (three), chlorpromazine, levomepromazine, zotepine (two for each), perospirone, blonanserin, sulpiride (one for each). No medication was modified during the study period. No severe side effect was observed throughout the trial. All participants tolerated the treatment well.

Intervention

We used a Soterix Medical 1 × 1 Transcranial Direct Current Low-Intensity Stimulator Model 1,300 A. For each session, the tDCS montage comprised placement of the anode over the left DLPFC and the cathode over the right supraorbital area (corresponding to F3 and FP2, according to the International 10–20 electroencephalography system), as previously investigated (27). Rubber electrodes were inserted in 35-cm^2 saline-soaked sponges, and were fixed with headband. We applied direct current of 2 mA for 20 min per session. Subjects underwent 10 tDCS sessions in 5 consecutive days, twice per day. On each day, tDCS intervention was performed approximately at 10 a.m. and 2 p.m.

Trained psychiatrists administered tDCS intervention. In order to maximize adherence, we provided all included patients and

TABLE 1 | Clinical characteristics of patients ($n = 28$).

Variables	Mean ± SD or *n*
Inpatient/outpatient	*22/6*
Male/female	*16/12*
Age, year	40.9 ± 9.8
Age at onset, year	23.6 ± 6.7
Duration of present illness, year	17.3 ± 9.9
Chlorpromazine equivalent dose of antipsychotics, mg/day	889.0 ± 587.1
Duration of education, year	13.8 ± 1.7
Premorbid IQ	99.6 ± 12.0
Global assessment of functioning	38.6 ± 6.9

their study partners with costs of transportation, and reminded and rescheduled all of the patients' visits if necessary.

Criteria for discontinuing interventions were as follows:

(1) In case patients withdraw informed consent to participate.
(2) In case severe adverse effects are observed.
(3) In case patients fail to undergo three consecutive sessions of tDCS.

Adjusting drugs were considered as a protocol deviation during the trial.

Outcome Measures

Subjects were assessed at baseline and 1 month after the last stimulation. Each evaluation was performed by experienced psychologists (Kazuki Sueyoshi and Crystal Lin). They were trained at a workshop.

Cognition

Cognitive function was assessed by the BACS. It is used to evaluate cognitive domains that are typically impaired in patients with schizophrenia, including verbal memory (Verbal Memory Task), verbal working memory (Digit Sequencing Task), motor/speed (Token Motor Task), verbal fluency (Verbal Fluency Task), attention/information processing (Symbol Coding Task), and executive function (Tower of London Task) (28). The higher scores represent better cognition. To provide a standard metric for combining test scores into domains and comparing performance over time, BACS scores were converted to *z*-scores (continuous variables) which show performances relative to those of healthy people (5). Alternative forms were used for the Verbal Memory Task and Tower of London Task at baseline and follow-up assessments.

Functional Capacity (Daily Living Skills)

Functional capacity was assessed by the UPSA-B (29). It is one of the measures most frequently used to evaluate daily living skills linked to cognitive function in schizophrenia (9, 29). Patients performed worse on the UPSA-B than do healthy individuals, a finding pertinent to some of the non-Western countries including Japan (9, 29). The UPSA-B consists of finance and communication subscales, which are continuous variables. Subscale scores of the two domains of the UPSA-B were converted into standard scores ranging from 0 to 50, so that the maximum of the total score was 100 (30). The higher scores represent better functional capacity. The validity of its Japanese version was confirmed (29).

Psychotic Symptoms

Psychotic symptoms were evaluated by the positive and negative syndrome scale (PANSS), commonly used for the assessment of psychotic symptoms of schizophrenia (31). The PANSS is a structured interview, consisting of positive, negative, and general psychopathology subscales (with scores ranging from 7 to 49, from 7 to 49, and from 16 to 112, respectively), whose scores are regarded as continuous variables. The higher scores represent more severe psychotic symptoms.

Depression

The Calgary depression scale for schizophrenia (CDSS), recommended as a brief and reliable tool for the assessment of severity of depression in schizophrenia (32), was used to assess depressive symptoms. The CDSS is a structured interview, consisting of items for depression, hopelessness, self-depreciation, guilty ideas of reference, pathological guilt, morning depression, early wakening, suicide, and observed depression. The score of each item ranges from 0 to 3 (i.e., discrete variable) (32). The higher scores represent more severe depressive state.

This study was approved by Ethical Committee of National Center of Neurology and Psychiatry, Tokyo, Japan. This was a single-arm, open-label study in which outcome measures were carried out before and after tDCS intervention (UMIN000015953). The patients first underwent a baseline assessment of the BACS, UPSA-B, PANSS, and CDSS; then they participated in the stimulation protocol consisting in twice-daily (10 a.m. and 2 p.m.) anodal tDCS over the left DLPFC and cathodal tDCS on the right superorbital area for 5 days, and were assessed again 1 month after the last stimulation. The study schedule is summarized in **Table 2**.

Statistical Analysis

Correlations between baseline values and their changes from baseline of BACS, UPSA-B, PANSS, and CDSS scores, were evaluated. Correlations were also examined for chlorpromazine equivalent dose of antipsychotics vs. changes from baseline of BACS, UPSA-B, PANSS, and CDSS scores, as well as change from baseline of UPSA-B scores vs. changes from baseline of BACS, PANSS, and CDSS scores.

Statistical analysis was conducted using STATA 14, created by StataCorp in TX, USA. We performed a per protocol approach for subjects who were followed-up until the end of study point. For continuous variables in the BACS, UPSA-B, PANSS, we used Student's *t*-test. For a discrete variable in the CDSS, we performed

TABLE 2 | Study schedule.

	Study period		
	Enrollment	**Intervention**	**Follow-up**
Time point	**Week 1**	**Week 2 (5 consecutive days)**	**Week 7**
Enrollment			
Eligibility screen	X		
Informed consent	X		
Sociodemographic characteristics	X		
Intervention			
tDCS (twice/day)		⟷	
Assessments			
BACS	X		X
UPSA-B	X		X
PANSS	X		X
CDSS	X		X
Adverse events	X	⟷	X

BACS, the brief assessment for cognition in schizophrenia; UPSA-B, the UCSD performance-based skills assessment-brief; PANSS, positive and negative syndrome scale; CDSS, Calgary depression scale for schizophrenia.

Wilcoxon signed-rank test. Pearson's product moment correlation coefficient was used for the relationship between clinical variables.

Monitoring

A systematic review revealed that the most common adverse events were itching, tingling, headache, burning sensation, and discomfort (33). A trained psychiatrist evaluated the safety with a semistructured checklist of these symptoms after each intervention. An independent safety monitoring committee ran an interim analysis for safety every week.

RESULTS

Table 3 shows outcome measures at baseline and 1 month after the last administration of tDCS.

Cognition

Significant improvement was found on BACS composite scores ($t = 4.23$, $p < 0.001$), as well as on verbal memory ($t = 4.53$, $p < 0.001$), motor/speed ($t = 2.47$, $p = 0.020$), and verbal fluency ($t = 2.10$, $p = 0.046$) subtests. Improvement of verbal memory was associated with a largest effect size ($d = 0.55$), while small to medium effect sizes were noted for motor/speed ($d = 0.44$), verbal fluency ($d = 0.36$), and composite scores ($d = 0.49$). No significant improvement was found on working memory, attention/information processing, and executive function.

Functional Capacity (Daily Living Skills)

Significant improvement was noted on UPSA-B finance ($t = 3.35$, $p = 0.002$) and communication ($t = 3.57$, $p = 0.001$) subscale scores, as well as on total scores ($t = 5.89$, $p < 0.001$), with medium to large effect sizes ($d = 0.61$, $d = 0.59$, and $d = 0.70$, respectively).

Psychotic Symptoms

Significant improvement was found on PANSS positive ($t = 2.31$, $p = 0.029$) and general psychopathology ($t = 2.35$, $p = 0.027$) subscale scores, with medium effect sizes ($d = 0.48$ and $d = 0.58$, respectively). On the other hand, no significant improvement was found for negative syndrome subscale scores.

Depression

Significant improvement was demonstrated on self-depreciation ($z = 2.46$, $p = 0.014$), morning depression ($z = 2.12$, $p = 0.034$), early wakening ($z = 3.11$, $p = 0.002$), and suicide ($z = 1.99$, $p = 0.046$) item scores, as well as total scores ($z = 2.83$, $p = 0.005$) of the CDSS, with small to medium effect sizes ($r = 0.33$, $r = 0.28$, $r = 0.42$, $r = 0.27$, and $r = 0.38$, respectively). On the other hand, depression, hopelessness, guilty ideas of reference, pathological guilt, and observed depression items were not significantly changed.

TABLE 3 | Outcome measures at baseline and 1 month after the treatment.

	Baseline, mean ± SD	Follow-up, mean ± SD	*t*-Value (degree of freedom) or *z*-value	*p*-Value	Effect size
BACS (*Z*-SCORE)					
Composite score	−1.86 ± 0.92	−1.40 ± 0.93	$t = 4.23$ (27)	**<0.001**	***d* = 0.49**
Verbal memory	−1.67 ± 1.06	−1.06 ± 1.14	$t = 4.53$ (27)	**<0.001**	***d* = 0.55**
Digit sequencing	−1.16 ± 1.38	−0.95 ± 1.37	$t = 1.52$ (27)	0.14	$d = 0.15$
Token motor	−3.27 ± 1.25	−2.73 ± 1.23	$t = 2.47$ (27)	**0.020**	***d* = 0.44**
Verbal fluency	−1.19 ± 1.05	−0.84 ± 0.89	$t = 2.10$ (27)	**0.046**	***d* = 0.36**
Symbol coding	−2.25 ± 1.22	−2.21 ± 1.44	$t = 0.25$ (27)	0.80	$d = 0.03$
Tower of London	−1.76 ± 2.03	−1.12 ± 2.16	$t = 1.88$ (27)	0.071	$d = 0.31$
UPSA-B					
Total	68.4 ± 14.8	79.0 ± 15.5	$t = 5.89$ (27)	**<0.001**	***d* = 0.70**
Finance	41.4 ± 8.1	45.8 ± 6.2	$t = 3.35$ (27)	**0.002**	***d* = 0.61**
Communication	27.1 ± 9.6	33.2 ± 11.1	$t = 3.57$ (27)	**0.001**	***d* = 0.59**
PANSS					
Positive syndrome	15.7 ± 5.7	13.1 ± 4.8	$t = 2.31$ (27)	**0.029**	***d* = 0.48**
Negative syndrome	14.9 ± 8.0	13.6 ± 6.7	$t = 1.24$ (27)	0.23	$d = 0.17$
General psychopathology	32 ± 8.1	28.3 ± 7.1	$t = 2.35$ (27)	**0.027**	***d* = 0.50**
CDSS					
Total	8.00 ± 4.97	5.36 ± 3.89	$z = 2.83$	**0.005**	***r* = 0.38**
Depression	0.79 ± 0.79	0.89 ± 0.92	$z = 0.79$	0.43	$r = -0.11$
Hopelessness	0.86 ± 0.93	0.57 ± 0.74	$z = 1.58$	0.11	$r = 0.21$
Self-depreciation	1.21 ± 1.17	0.71 ± 0.85	$z = 2.46$	**0.014**	***r* = 0.33**
Guilty ideas of reference	0.75 ± 1.04	0.50 ± 0.64	$z = 0.39$	0.39	$r = 0.11$
Pathological guilt	0.82 ± 0.90	0.57 ± 0.88	$z = 1.58$	0.11	$r = 0.21$
Morning depression	0.82 ± 0.72	0.61 ± 0.63	$z = 2.12$	**0.034**	***r* = 0.28**
Early wakening	1.68 ± 1.25	1.00 ± 0.86	$z = 3.11$	**0.002**	***r* = 0.42**
Suicide	0.61 ± 0.83	0.25 ± 0.52	$z = 1.99$	**0.046**	***r* = 0.27**
Observed depression	0.46 ± 0.51	0.25 ± 0.44	$z = 1.90$	0.058	$r = 0.25$

BACS, The Brief Assessment for Cognition in Schizophrenia; UPSA-B, The UCSD Performance-based Skills Assessment-Brief; PANSS, Positive and Negative Syndrome Scale; CDSS, Calgary Depression Scale for Schizophrenia.

Correlation

No significant correlation was noted between baseline values and their changes from baseline of BACS and UPSA-B scores. In contrast, significant negative correlations were demonstrated between baseline values vs. their changes from baseline of PANSS positive subscales ($r = -0.65$, $p < 0.001$, **Figure 1**), negative subscales ($r = -0.56$, $p < 0.002$, **Figure 2**), general psychopathology subscales ($r = -0.64$, $p < 0.001$, **Figure 3**), and CDSS total scores ($r = -0.66$, $p < 0.001$, **Figure 4**). No significant correlation was found between chlorpromazine equivalent dose of antipsychotics vs. changes from baseline of BACS, UPSA-B, PANSS, and CDSS scores. The same applied to correlations between change from baseline of UPSA-B scores vs. changes from baseline of BACS, PANSS, and CDSS scores.

DISCUSSION

To our knowledge, this study was the first to suggest the ability of tDCS to improve daily living skills linked to cognition (functional capacity, measured by UPSA-B), as well as depressive symptoms (measured by the CDSS) in patients with schizophrenia. Also, this study was the first to indicate the improvement of functional capacity after 5-day administration of tDCS, which was not correlated with the change of cognition, psychosis, and depression. At the same time, tDCS was found to enhance cognition in these subjects.

The results obtained in this trial are consistent with those from other studies indicating that tDCS may be effective to improve cognition in healthy controls (34–36) and patients with schizophrenia (18, 22, 23, 37). In a previous study, five sessions of tDCS in consecutive days, with the anode over F3 and the cathode over FP2, enhanced working memory and attention/vigilance to a greater extent than did sham-treatment in patients with schizophrenia (24). In our study, significant effects of tDCS were noted in the domains of verbal memory

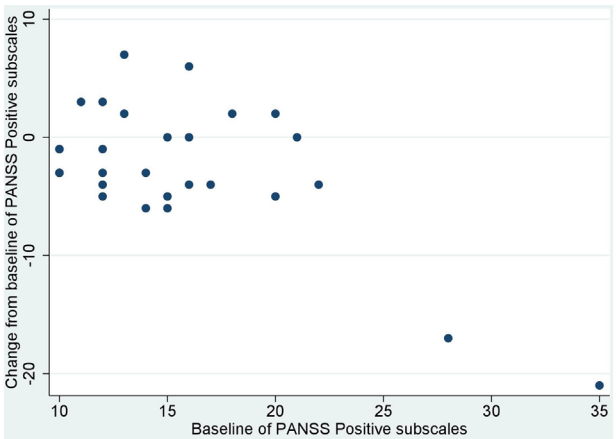

FIGURE 1 | Correlation between the baseline and change from baseline of positive and negative syndrome scale (PANSS) positive subscales ($r = -0.65$, $p < 0.001$).

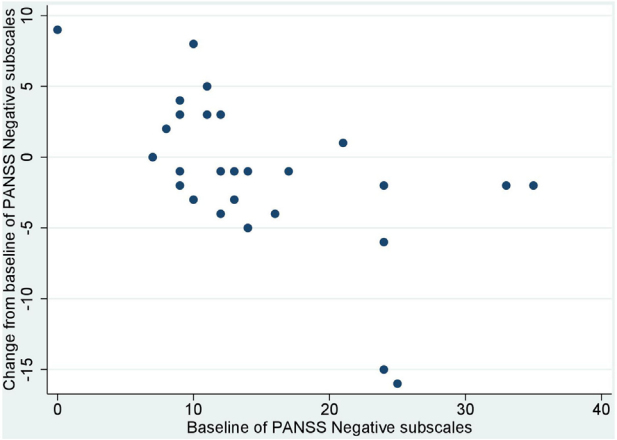

FIGURE 2 | Correlation between the baseline and change from baseline of positive and negative syndrome scale (PANSS) negative subscales ($r = -0.56$, $p < 0.002$).

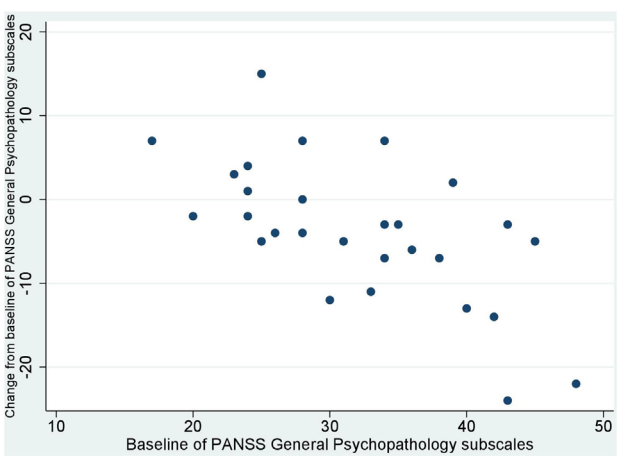

FIGURE 3 | Correlation between the baseline and change from baseline of positive and negative syndrome scale (PANSS) general psychopathology subscales ($r = -0.64$, $p < 0.001$).

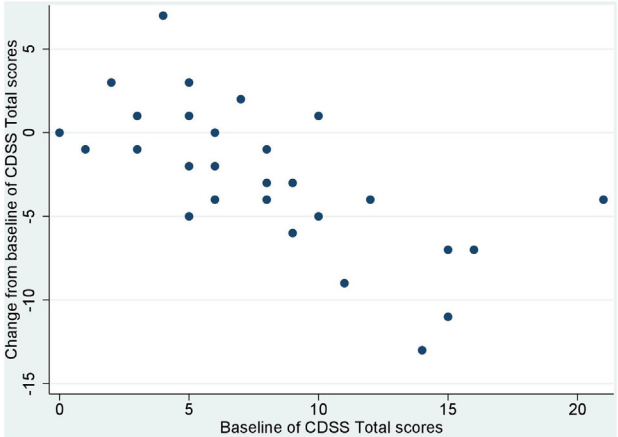

FIGURE 4 | Correlation between the baseline and change from baseline of Calgary depression scale for schizophrenia (CDSS) total scores ($r = -0.66$, $p < 0.001$).

(with different versions of word lists at baseline and follow-up), with a small to medium effect size, which suggests that tDCS moderately promotes cognitive function in schizophrenia. On the other hand, no significant improvement was demonstrated in working memory. This discrepancy may be due to the difference in the study design, treatment regimen (5 session of tDCS in consecutive days in the previous study, while 10 sessions of tDCS in 5 consecutive days in our study), and/or sample size. It is also possible that an effect on working memory might have vanished in 1-month follow-up period. In this sense, the inclusion of data on the cognitive outcomes immediately after the last stimulation could have provided more detailed information. While a previous study evaluated working memory immediately after the last tDCS (24, 38), the measurement of the BACS and UPSA-B at this time-point were not included in our protocol. This was because evaluating the BACS and UPSA-B just 1 week after baseline assessments with the same tests could produce learning effects.

The mechanisms by which tDCS affects cognitive function in schizophrenia may be explained in several ways. Functional connectivity of the frontoparietal control network and interhemispheric connectivity are decreased in schizophrenia patients, likely to be related to impairment of higher order cognitive task-related activities and disruption of the default mode network (10–12). Several studies demonstrated that tDCS alters functional connectivity in, for example, the default mode network and the frontoparietal control network, in healthy subjects (39, 40). Also, a case study reported that tDCS changed functional brain connectivity in the anterior part of the default mode network (41). Furthermore, Kim et al. reported neurophysiological evidence that tDCS modulates sensory gating in schizophrenia (42). Neurochemically, the after-effects of anodal tDCS are considered to depend on modulation of both GABAergic and glutamatergic synaptic transmissions (17). Further investigations of biological measures are warranted to elucidate the mechanisms by which tDCS exerts pro-cognitive effects.

tDCS was also found to improve daily living skills linked to cognition (functional capacity), measured by the UPSA-B with medium to large effect sizes, in schizophrenia. To our knowledge, there has been no attempt to elucidate the effect of tDCS on this level of functional outcomes in psychiatric conditions. In view of the association between performance on the UPSA-B and real-world functional outcomes (43), the result reported here suggests the ability of tDCS to enhance social outcome in schizophrenia.

Data from this study also suggest the ability of tDCS to ameliorate depressive mood, evaluated objectively by the CDSS (32), in patients with schizophrenia. Results from a meta-analysis indicate that tDCS is effective in treating patients with major depressive disorder, with an effect size comparable with those reported for repetitive transcranial magnetic stimulation and antidepressant drugs (44). Some domains in depressive symptoms were improved with small to medium effect sizes, similar to the case in patients with major depressive disorder (44). The antidepressant effect of tDCS may be related to hypoactivity of the left DLPFC, which is likely to be restored by anodal tDCS (45). The results presented in the current study are consistent with this hypothesis, and may provide a strategy to ameliorate treatment-resistant depressive symptoms in patients with schizophrenia.

tDCS was found to improve positive symptoms and general psychopathology with medium effect sizes, which is advantageous for patients suffering from psychotic symptoms. So far, two studies have attempted to see the effect of tDCS on psychopathology, as measured by the PANSS. Brunelin et al. did not find a significant effect on either positive or negative symptoms. These authors placed the anodal electrode over a point midway between F3 and FP1 and the cathodal electrode over a point midway between T3 and P3 (46). On the other hand, Smith et al. observed significant improvement only in negative symptoms. These investigators placed the anode over F3 and the cathode over FP2 (24). Taken together, further studies to seek optimal methods of tDCS to ameliorate psychotic symptoms are needed.

Changes of cognition and daily living skills were not correlated with their baseline scores. In contrast, the improvements of positive symptoms, negative symptoms, general psychopathology, and depression were correlated with their baseline scores. These observations suggest the lack of ceiling effects of tDCS on cognition and daily living skills. Also, the lack of significant correlation between chlorpromazine equivalent dose of antipsychotics vs. the improvement of cognition, functional outcome, psychotic symptoms, and depression suggests that tDCS may improve these outcome measures regardless of the dose of antipsychotics. Furthermore, the lack of significant correlation between the improvement of functional capacity vs. cognition, positive symptoms, and depression, indicates that the observed change of functional capacity was independent of these clinical variables. However, the possibility of unobserved confounders cannot be ruled out completely with the current study design.

The limitations of this study should be noted here. The lack of blinding might have produced practice (repeated-measure) effect in some measures used. To circumvent this issue, alternate forms were used for verbal memory (word list learning task) and executive function (Tower of London task) in the BACS at the follow-up assessment. Therefore, the pro-cognitive effect of tDCS on verbal memory may not be attributable to repeated-measure effect. In addition, a small sample of this study may raise caution in concluding that these results represent effects in the population. Also, the lack of randomization, controlled group, and blinding might have produced placebo effects. Inclusion of a sham-controlled group could have provided a definitive conclusion. Accordingly, we are initiating a randomized sham-controlled trial with a larger sample (Narita, et al. submitted; UMIN000028224).

In conclusion, the results of the present study suggest the efficacy of tDCS on cognition, daily living skills, and depression. These results may add to the concept that tDCS provides a strategy to enhance functional outcomes in patients with schizophrenia.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of Ethical Guideline for Clinical Researches, Ministry of

Health, Labor and Welfare with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Ethical Committee of National Center of Neurology and Psychiatry.

AUTHOR CONTRIBUTIONS

ZN managed the literature searches, undertook the statistical analysis, and wrote the first draft of the manuscript. TI, TS, and ZN administered tDCS. TS designed the study and wrote the protocol. CL and KS conducted clinical assessments. All authors made substantial contribution, drafted the manuscript, and approved the final manuscript.

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PROTOCOLS
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Effect of Transcranial Direct Current Stimulation on Functional Capacity in Schizophrenia: A Study Protocol for a Randomized Controlled Trial

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Schizophrenia patients elicit a wide range of psychopathology, including psychotic symptoms, mood symptoms, and cognitive impairment. Functional capacity is defined as the ability to perform everyday living skills, which is linked to cognition and real-world functional outcome. In a previous open trial, we demonstrated that transcranial direct current stimulation (tDCS), one of the neuromodulation methods, improved cognition and functional capacity in 28 patients with schizophrenia. However, since it was a pilot study, a controlled trial is needed. Therefore, we present a study protocol for a randomized controlled trial designed to evaluate the effect of tDCS on functional capacity in patients with schizophrenia. This is a two-arm, parallel-design, randomized controlled trial, in which patients and assessors will be blinded. Patients meeting DSM-5 criteria for schizophrenia will be enrolled and randomized to receive either active or sham stimulation (with 10 sessions in five consecutive days). Functional capacity will be evaluated by the UCSD Performance-based Skills Assessment-Brief as primary outcome. Cognition, as measured by the Brief Assessment of Cognition in Schizophrenia, and psychotic symptoms, as measured by the Positive and Negative Syndrome Scale, will also be evaluated. Data will be collected at baseline, immediately after the last stimulation, and 1 and 2 months thereafter. If active stimulation elicits greater effects compared with those of sham stimulation, it may add to the efforts to improve functional outcomes by neuromodulation in patients with schizophrenia.

Trial registration: UMIN000028224; https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000032305.

Keywords: neuromodulation, daily-living skills, cognition, transcranial direct current stimulation, functional outcome, randomized controlled trial

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INTRODUCTION

Schizophrenia patients elicit a wide range of psychopathology, including psychotic symptoms, mood symptoms, and cognitive impairment (1–3). Several domains of cognitive function such as some types of memory, executive function, verbal fluency, and attention/information processing are impaired in schizophrenia (1, 2). Functional capacity is defined as the ability to perform everyday living skills, such as financial competence and communication in controlled and observational settings (3). By contrast, social function is influenced by several factors, such as opportunities and incentives in daily

life (4). These levels of outcomes (cognitive function, functional capacity, and social function) have been reported to be related to each other (5, 6).

The UCSD Performance-based Skills Assessment-Brief (UPSA-B) is a scale of functional capacity linked to cognitive functioning in schizophrenia (5, 7). Patients with the illness demonstrate significantly lower scores on this scale compared with healthy controls, a finding pertinent to some of the non-Western countries, including Japan (5, 7).

Neuromodulation is defined as alterations of neural activity with targeted delivery of a stimulus, such as electrical stimulation or chemical agents, to specific neurological sites in the body. Neuromodulation techniques range from non-invasive approaches, e.g., transcranial magnetic stimulation, to invasive (implanted) devices, e.g., spinal cord stimulation and deep brain stimulation. For instance, transcranial direct current stimulation (tDCS) is a feasible and safe method, using weak and direct electrical current to the brain through electrodes (8, 9). Typically, two electrodes are placed over the scalp, through which anodal and cathodal stimulation increases and decreases cortical excitability, respectively. With this mechanism, tDCS has been suggested to modulate corticosubcortical/corticocortical pathways (10, 11).

tDCS has been shown to improve several domains of cognitive function in healthy subjects, stroke patients, and elderly individuals (12–17). Also, some studies reported facilitative effects of tDCS on learning memory, working memory, and verbal fluency in schizophrenia (18–20). Moreover, one sham-controlled randomized study has revealed that tDCS improved performance on the MATRICS Consensus Cognitive Battery in schizophrenia (21). On the other hand, little information is available about the effect of tDCS on functional capacity, as evaluated by a specific assessment tools, such as the UPSA-B.

In a previous open trial, we demonstrated the ability of tDCS to improve functional capacity, as well as depressive symptoms, in patients with schizophrenia (22). However, since this was a pilot study with a single arm, conducting a controlled trial is desirable. Therefore, we present a study protocol for a randomized controlled trial designed to evaluate the efficacy of tDCS on functional capacity in patients with schizophrenia.

MATERIAL AND EQUIPMENT

Study Design

This is a single-center trial at Nacional Center of Neurology and Psychiatry, Tokyo, Japan (**Figure 1**). A two-arm, parallel-design, randomized controlled trial is planned, in which patients and raters will be blinded. Participants will be randomized with 1:1 ratio to either active or sham tDCS group with computer-generated sequence in the Electronic Data Capture (EDC) system. The superiority of active tDCS to sham tDCS will be investigated. Subjects will receive 10 sessions of active/sham tDCS in five consecutive days (twice per day). A participant's allocation will be revealed by the principle investigator after the study endpoint. Results of the trial will be communicated by the study coordinators when requested.

Participants

Inpatients or outpatients treated at National Center Hospital, National Center of Neurology and Psychiatry will be enrolled. Subjects will be recruited by referrals from treating psychiatrists.

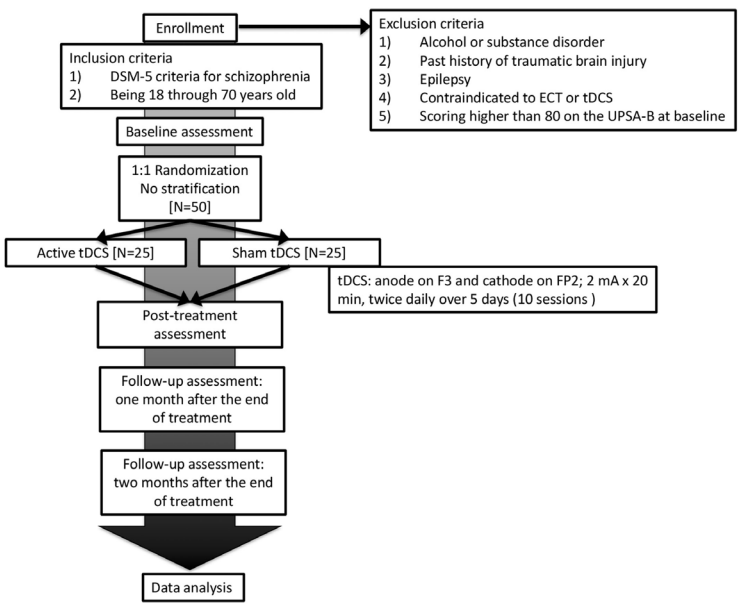

FIGURE 1 | Flowchart summarizing the trial procedure. ECT, electroconvulsive therapy; tDCS, transcranial direct current stimulation.

They must provide written informed consent before starting the trial.

Subjects must meet the following inclusion criteria:

(1) DSM-5 criteria for schizophrenia
(2) Being 18 through 70 years old

Patients with any of the following conditions will be excluded from the study:
(1) Alcohol or substance disorder
(2) Past history of traumatic brain injury
(3) Past history of epilepsy
(4) Contraindicated to electroconvulsive therapy or tDCS
(5) Scoring higher than 80 on the UPSA-B at baseline

The dose of neuroleptics will not be changed during the study period. In our pilot study (22), mean and SD of change from baseline of the UPSA-B was 11.68 (9.84) in patients scoring lower than 80 at baseline. We conservatively hypothesized that 9.00, the lower limit of 50% confidence interval of mean change from baseline in the pilot study, would be the mean difference between two groups in this study. In addition, Pearson correlation coefficient between the change and baseline value of the UPSA-B was estimated as −0.340. In these conditions, with a power of 0.9 for the primary analysis, an approximate number of 24 per group were estimated. Thus, considering study dropouts, a total sample of 50 was determined to be included.

Intervention

Direct current will be transferred by 35-cm^2 saline-soaked sponge electrodes and delivered by Soterix Medical 1 × 1 Transcranial Direct Current Low-Intensity Stimulator Model 1300A. For each session, the tDCS montage will comprise placement of the anode over the left dorsolateral prefrontal cortex and the cathode over the contralateral supraorbital area, which corresponds to F3 and FP2 area, according to the International 10–20 electroencephalography system. We will apply 10 sessions of direct current of 2 mA for 20 min in five consecutive days (twice per day, 10:00 a.m. and 2:00 p.m.). The dose and frequency of stimulation were determined based on the pilot study (22).

For the sham group, the device will be turned off after 1 min of active stimulation. The electrode position and all the other procedures, including electrode moisture and checking the contact, will be identical to the conditions for the active-stimulation group. The display of the device will be kept outside participants' vision field, and the device will be turned off blinded to subjects. A controlled study reports blinding integrity of tDCS and pharmacological treatment was comparable (23). The assessors and patients will be blinded to the treatment, and the contact between participants will be avoided to enhance the effect of study blinding.

Trained psychiatrists will administer tDCS. Since they will not be blinded, his or her interaction with participants will be minimized. Also, the experimenters will not participate in the assessment of outcome measures or any other aspects of the trial. To improve adherence, we will provide all consenting participants with costs of transportation and will remind and reschedule the visits of participants if necessary.

Outcome Measures

Patients will be assessed after being informed of the objectives of the study and providing their informed consent to participate. Data will be collected following an assessment that will be implemented at baseline, immediately after the last stimulation, and 1 and 2 months thereafter (see **Table 1**). Baseline and follow-up evaluations will be performed by experienced psychologists blinded to group allocation.

Functional Capacity (Daily-Living Skills)

The primary outcome is functional capacity evaluated by the UPSA-B (7), which consists of Finance and Communication subscales.

Cognition

Cognitive function will be assessed by the Brief Assessment of Cognition in Schizophrenia (BACS), which includes tests of verbal memory (Verbal Memory Task), verbal working memory (Digit Sequencing Task), motor/speed (Token Motor Task), verbal fluency (Verbal Fluency Task), attention/information processing (Symbol Coding Task), and executive function (Tower of London Task). To provide a standard metric for combining test scores into domains and comparing performance over time, BACS scores will be converted to *z*-scores, which shows relative outcomes compared with those of healthy people (1). Alternative forms will be used for Verbal Memory Task and Tower of London Task at baseline and follow-up assessments.

Psychotic Symptoms

Psychotic symptoms will be evaluated by the Positive and Negative Syndrome Scale (PANSS), commonly used for the assessment of psychotic symptoms of schizophrenia (24). It consists of Positive Syndrome, Negative Syndrome, and General Psychopathology subscales.

To ensure the success of blinding, we will ask patients to guess whether the treatment was active or sham after the stimulation procedure has been completed.

STEPWISE PROCEDURES

This protocol is presented in accordance with the 2013 SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) Statement, which was developed to provide guidance in the form of a checklist of recommended items to include in a clinical trial protocol to help improve the content and quality (25). This study was approved by Ethical Committee of National Center of Neurology and Psychiatry.

The schedule of enrollment, interventions, and assessments is summarized in **Table 1**. Participants will be recruited mainly by referrals from psychiatrists in National Center of Neurology and Psychiatry, Tokyo, Japan. We expect that two patients can be recruited per month on average, and that it will be possible to recruit 50 participants in 25 months.

All raters are well trained. All data will be administered in the EDC system, HOPE eACReSS, created by Fujitsu, Tokyo, Japan. Allocation and other identifiable data of subjects will be stored in a computer disconnected from Internet.

TABLE 1 | Study schedule.

	Study period						
	Enrollment	Intervention				Follow-up 1	Follow-up 2
Time point	Week 1	Week 2				Week 6	Week 10
		Day 1	Day 2	Day 3	Day 4	Day 5		
Enrollment								
Eligibility screen	X							
Informed consent	X							
Sociodemographic characteristics	X							
Intervention								
Transcranial direct current stimulation (twice/day)		←	—	—	—	→		
Assessments								
UPSA-B	X					X	X	X
BACS	X					X	X	X
PANSS	X					X	X	X
Adverse events	X	←	—	—	—	→	X	X

UPSA-B, the UCSD Performance-based Skills Assessment-Brief; BACS, the Brief Assessment of Cognition in Schizophrenia; PANSS, Positive and Negative Syndrome Scale.

A review of previous studies indicates that most common adverse events included itching, tingling, headache, burning sensation, and discomfort (26). Experienced psychiatrists will check adverse effects before/immediately after every session, and evaluate the safety at every visit during the intervention. Data supervision using the EDC system will be conducted by an independent team of data managers and monitors.

ANTICIPATED RESULTS

As discussed earlier, we anticipate that 9.00 will be the mean difference in the UPSA-B between two groups. Statistical analysis will be conducted using SAS 9.4, created by SAS Institute Inc., NC, USA. We will handle missing data with last observation carried forward method as an intention-to-treat analysis for all participants allocated. We will also perform a per protocol approach as a sensitivity analysis for the comparison of the results. For the UPSA-B, BACS, and PANSS, we will use analysis of covariance regarding each value at baseline as a covariate.

Functional capacity, or daily-living skills, has been reported to provide one of the most important factors affecting social consequences in patients with schizophrenia (6, 27). As stated before, tDCS is a safe method of brain stimulation and has been reported to improve several domains of cognition in schizophrenia (18–22). In addition, our pilot open study (22) demonstrated tDCS improved functional capacity, as measured by the UPSA-B. So far, no controlled trial has been performed to investigate the effect of tDCS on this level of functional outcome. Therefore, the randomized controlled trial described in this article is expected to provide a strategy to enhance social consequences in patients with schizophrenia.

The topic of adherence might be regarded as a potential pitfall in this protocol. However, as mentioned before, by adding costs of transportation for all included patients to the study budget, we plan to compensate for this issue. Also, the study coordinator will remind and reschedule all visits of participants as needed.

We believe that this is a well-designed controlled trial to test the ability of tDCS to improve an important determinant of outcome in patients with psychiatric disorders. Even if the results do not prove our hypothesis, the gathered data will contribute to a field that has not been widely studied.

ETHICS STATEMENT

The protocol was presented to an institutional review board for approval (National Center of Neurology and Psychiatry Ethics Committee). The principal investigator (TS) will be responsible for conducting the informed consent process with all the study participants. All subjects must give consent to participate in the trial. Any relevant changes in the study protocol and/or the informed consent will be sent to the institutional review board as a protocol amendment. Identities of all subjects will be protected with an individual code. The protocol was registered in UMIN before starting the trial.

AUTHOR CONTRIBUTIONS

TS initiated the study. KM, TS, and ZN designed it and wrote the protocol. ZN and KS managed the literature searches and wrote the first draft of the manuscript. TI, TS, and ZN will administer tDCS. All the authors made substantial contribution, drafted the manuscript, and approved the final manuscript.

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REVIEW
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Brain Stimulation in Alzheimer's Disease

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Brain stimulation techniques can modulate cognitive functions in many neuropsychiatric diseases. Pilot studies have shown promising effects of brain stimulations on Alzheimer's disease (AD). Brain stimulations can be categorized into non-invasive brain stimulation (NIBS) and invasive brain stimulation (IBS). IBS includes deep brain stimulation (DBS), and invasive vagus nerve stimulation (VNS), whereas NIBS includes transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), electroconvulsive treatment (ECT), magnetic seizure therapy (MST), cranial electrostimulation (CES), and non-invasive VNS. We reviewed the cutting-edge research on these brain stimulation techniques and discussed their therapeutic effects on AD. Both IBS and NIBS may have potential to be developed as novel treatments for AD; however, mixed findings may result from different study designs, patients selection, population, or samples sizes. Therefore, the efficacy of NIBS and IBS in AD remains uncertain, and needs to be further investigated. Moreover, more standardized study designs with larger sample sizes and longitudinal follow-up are warranted for establishing a structural guide for future studies and clinical application.

Keywords: brain stimulation, Alzheimer's disease (AD), transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), electroconvulsive treatment (ECT), magnetic seizure therapy (MST), cranial electrostimulation (CES)

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INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and accounts for most of dementia in the elderly (1, 2). The prevalence of dementia due to AD in adults aged more than 60 years was 4.02% (3). 35.6 million adults were victims of dementia in the world in 2010, and the number is estimated to be 65.7 million in 2030 (4). AD is costly, with worldwide spending estimated to be US $422 billion in 2009 (5). Currently, cholinesterase inhibitors and N-methyl-D-aspartate receptor partial antagonist, memantine, are the main pharmacologic treatments for patients with AD. However, these treatments are accompanied by adverse effects and the response is limited (6). Therefore, alternative treatments require urgent development.

The use of brain stimulation has recently garnered considerable clinical and academic interest. In this review, we explore invasive brain stimulation (IBS), non-invasive brain stimulation (NIBS), and their potential applications in the AD field. IBS includes deep brain stimulation (DBS) and invasive VNS. NIBS includes transcranial magnetic stimulation (TMS), transcranial direct

current stimulation (tDCS), transcranial alternating current stimulation (tACS), electroconvulsive treatment (ECT), magnetic seizure therapy (MST), cranial electrostimulation (CES), and non-invasive vagus nerve stimulation (VNS).

INVASIVE STIMULATION METHODS

Deep Brain Stimulation

A deep brain stimulation (DBS) system includes electrode leads, wires, and a pulse generator. Neurosurgeons implant electrode leads in the brain and pulse generator below the collar bone. Both are connected by wires which are tunneled underneath the skin. To date, DBS is the Food and Drug Administration (FDA)-approved for the management of Parkinson's disease, and essential tremor. In addition, this device has also been approved for refractory obsessive-compulsive disorder and dystonia symptoms as a humanitarian device exemption (7–10).

The first DBS trial for AD was performed in 1984, and the targeted brain region was the nucleus basalis of Meynert (NBM). Turnbull and colleagues found no improvement in memory or cognition, but the researchers noted preserved cortical glucose metabolic activity in the left parietal and left temporal lobes as well as the partial arrest of deterioration in the left frontal area (11). However, no subsequent trials of DBS for AD were performed for 26 years. When using DBS of the fornix to treat obesity in 2008, Hamani et al. discovered "deja vu-like" sensations during surgery. The researchers also found improvements in spatial associative learning and verbal learning after 3 weeks of DBS treatment (12). Therefore, in 2010, a Phase I trial was implemented to investigate DBS treatment of the fornix/hypothalamus in six adults with early AD. Two patients experienced autobiographical experiential phenomena during surgery. Moreover, after 12-month DBS treatment, the patients exhibited improved memory, reduced cognitive decline, reversed glucose metabolism (13), and increased hippocampal volume (14).

Because the Phase I trial demonstrated the promising effects of DBS of the fornix, the same group enrolled 42 participants with mild, probable AD for Phase II study (15). In this randomized double-blind trial, 21 participants in "off stimulation group" did not receive stimulation, whereas 21 participants in "on stimulation group" underwent continuous DBS stimulation for 12 months. Subsequently, all participants receive stimulation for 12 months. However, the first year of this trial revealed no significant differences of cognitive scores between these two groups. Moreover, this trial revealed that the cognitive function of patients aged <65 years significantly worsened after 1 year of DBS, whereas patients aged ≥ 65 exhibited a slight improvement in cognitive function. In terms of safety, the authors observed four acute serious safety events and three long-term serious events, and suggested DBS was well-tolerated (15).

In addition to the Phase I (13) and Phase II trials (15) of fornix DBS in North America, DBS for AD studies have also been conducted in Europe. In France, Fontaine et al. reported that after 12 months of fornix DBS, a patient with mild cognitive decline showed stabilized cognitive performance and increased mesial temporal lobe metabolism (16). In Germany, Kuhn and colleagues delivered bilateral DBS over the NBM of 6 participants with mild to moderate AD (17). The authors used the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) to evaluate the patients' cognition. Four of the six patients were considered responders 12 months after surgery. Moreover, several participants exhibited increased temporal and amygdalohippocampal glucose metabolism after stimulation for almost 1 year. Based on these promising findings, Kuhn et al. performed continuous DBS of the NBM in two patients of an average age younger than that of the patients in the aforementioned Phase I trial, and who both had lower baseline ADAS-Cog scores (18). One patient's cognition had worsened after 26 months according to ADAS-Cog and Mini–Mental State Examination (MMSE) scores, whereas the other patient had a stable ADAS-Cog score and improved MMSE score after 28 months. Hardenacke et al. (19) evaluated the findings of the Phase I trial (17) and 2 new patients and suggested that performing DBS of the NBM at a younger age and earlier disease stage may favorably influence cognitive function and disease progression.

Invasive Vagus Nerve Stimulation

Vagus nerve stimulation (VNS) modulates brain network activity by stimulating tenth cranial nerve. The stimulation of tenth cranial nerve (vagus nerve) can be performed using two methods: direct invasive stimulation and indirect transcutaneous non-invasive stimulation. The invasive VNS (iVNS) system includes a pulse generator and electrodes. Surgeons attach electrodes to the left-side vagus nerve and connect them to the pulse generator which is implanted in the left thoracic region. The pulse generator delivers programmable electrical stimulation to the vagus nerve (20, 21).

Two studies have investigated the relationship between iVNS and AD (21, 22). In Sweden, researchers enrolled 10 patients with AD (22). Each patient received surgery to implant a pulse generator, which deliver programmable signals to the left-side tenth cranial nerve. The initial settings were frequency 20 Hz, pulse width 500 μs, and current 0.25 mA. The stimulation was on for 30 s followed by a pause for 5 min. After 3 months of treatment, they found the response rates were 70% (seven of 10 patients) on the ADAS-Cog and 90% (nine of 10 patients) on the MMSE. The response rates remained similar after 6 months of the iVNS treatment. Adverse effects of iVNS were transient and mild.

Therefore, based on these promising findings, the same research team recruited another seven patients with AD. The researchers followed up these total 17 patients for at least 1 year (21). They found that 1 year after iVNS treatment, the score of the ADAS-Cog in seven patients did not decline or even increase, while the score of the MMSE in 12 patients did not decline or even improve compared with baseline. These two small trials revealed that invasive VNS was well-tolerated and improved specific cognitive functions in MMSE and ADAS-Cog after 1 year and 3 months of treatment, respectively.

NON-INVASIVE STIMULATION METHODS

Transcranial Magnetic Stimulation

In 1985, Barker and colleagues first reported transcranial magnetic stimulation (TMS) on motor cortex (23). TMS delivers a rapidly changing current through a coiled wire encased in plastic above the scalp. Based on Faraday's law of electromagnetic induction, this results in a magnetic field across the skull, and subsequently generate an electric current in the targeted brain regions (24, 25). The stimulation intensity determines the dosage according to the individual's motor-evoked potential threshold, and modulates the cortical neurons (26). Repetitive TMS (rTMS) delivers trains of several pulses at the same intensity over a period of time. rTMS protocols comprises high frequency ($\geq$ 5 Hz) and low-frequency ($\leq$1 Hz) as well as various types of stimulation bursts such as theta-burst stimulation (TBS) (25).Generally, higher frequencies (e.g., 20 Hz) may increase cortical excitability, whereas lower frequencies (approximately 1 Hz) may inhibit cortical excitability (24–26). However, low-frequency TMS may not always result in inhibition (27). Moreover, in the motor cortex, continuous TBS causes inhibitory aftereffects, whereas intermittent TBS causes excitatory aftereffects (28). Different stimulation protocols produce different aftereffects of different durations. For example, TBS protocols yield the longest aftereffects of up to 8 h, whereas long or multiple rTMS trains yield aftereffects of less than 1 h (29, 30).

Several trials and reviews have suggested that rTMS may be beneficial for various cognitive functions in patients with AD (31–41). In Italy, Cotelli and colleagues recruited 15 patients with AD and reported that rTMS administered to the bilateral dorsolateral prefrontal cortexes (DLPFCs) enhanced accuracy in action naming (31). Based on this promising finding, this research team launched another trial of 24 adults with AD of varying severity (a mild AD group and moderate-to-severe AD group) (32). Similar to previous findings, the researchers revealed that rTMS over bilateral DLPFCs enhanced action naming in these two groups. Moreover, they noted significantly improved object naming accuracy in participants with moderate-to-severe AD but not in participants with mild AD. However, these two studies have adopted only single rTMS sessions to evaluate the immediate cognitive effects on patients with AD. The long-term cognitive effect on patients with AD remains unknown. Therefore, they further conducted a multiple-baseline trial of 10 patients with AD divided into two groups (33). The first group underwent high-frequency (20 Hz) rTMS over the left DLPFC, five times a week for 4 weeks, whereas the second group received placebo rTMS for 2 weeks, followed by high-frequency rTMS for 2 weeks. After 2-week therapy, the authors observed participants receiving real rTMS had significant higher rates of correct responses than those receiving placebo rTMS. In addition, the researchers noted that 8 weeks after the end of treatment, both groups still had lasting improved performance (**Table 1**).

In Egypt, Ahmed and colleagues recruited 45 participants with AD and randomly assigned them into three groups (36). The first group underwent five sessions of high-frequency (20 Hz) rTMS over the DLPFC. The second group received low-frequency (1 Hz) rTMS, while the third group underwent sham rTMS. The results showed a significant improvement in MMSE after applying high-frequency (20 Hz) rTMS. In addition to the DLPFC, Eliasova and colleagues applied high-frequency (10 Hz) rTMS over the right inferior frontal gyrus (IFG) (39). Ten participants with early AD underwent 10 Hz rTMS over the right IFG and vertex in random order, 2250 stimuli per session. The authors found a significant improvement in in the Trail Making Test parts A and B after applying 10 Hz rTMS over the right IFG.

In China, Zhao and colleagues included 30 participants with AD, and assigned 17 participants into the rTMS group, 13 participants into the sham group (38). Patients of the rTMS group underwent 30 sessions of 20 Hz rTMS over three brain regions for 6 weeks, whereas the control group received placebo stimulation. Three brain regions included posterior temporal T5/T6 and parietal P3/P4, based on the 10–20 electroencephalogram system. The authors found a significant improvement in ADAS-Cog, MMSE, as well as World Health Organization and University of California–Los Angeles Auditory Verbal Learning Test after applying rTMS over the three brain regions for 6 weeks.

In Israel, Bentwich and colleagues developed a combined treatment of high-frequency rTMS and cognitive training (rTMS-COG) (34). Eight patients with AD underwent daily rTMS-COG treatment for 6 weeks, and then maintained two sessions per week for 3 months. High-frequency rTMS were delivered over six specific brain regions including Broca's area, Wernicke's area, bilateral DLPFC, and right and left parietal somatosensory association cortices (R-pSAC and L-pSAC, respectively). The average ADAS-Cog scores significantly improved from 22.5 at baseline to 18.3 at 6-week and 18.5 at 4.5-month. Clinical Global Impression of Change (CGIC) scores also improved by 1.0 and 1.6 points, respectively. Based on these positive results, the same group recruited 15 patients with AD and randomly assigned them into two groups (37). Seven participants underwent rTMS-COG one hour per day, five times a week for 6 weeks, followed by two times a week for three months. Eight participants in the placebo group received sham treatment. The authors found an improvement in ADAS-Cog and CGIC after applying rTMS-COG for 6 weeks and 4.5 months. However, the effects of rTMS and cognitive training are difficult to differentiate because these trials lacked a control group receiving only cognitive training. Moreover, they stimulated six brain regions instead of only the DLPFC. The cognitive effects of stimulation on different regions remain unclear. Therefore, a recent review suggested that further trials are required to use a larger sample size to investigate the synergic effects of rTMS and cognitive training and investigate the cognitive effects on different brain regions (42).

Transcranial Direct Current Stimulation

The transcranial direct current stimulation (tDCS) delivers electric current, typically ranged 1 to 2 mA, through two or more electrodes placed on the scalp (43). Researchers put anodal and cathodal electrodes into holding bags and moisten them with saline or conductive gel to lower electric resistance. Two electrodes are placed over the head based on the international 10–20 point system. This week current penetrates skull and modulates neural activity of targeted brain regions (44). Generally, anodal tDCS increases cortical excitability in the

TABLE 1 | Clinical trials using rTMS as therapeutic tool in Alzheimer's disease.

Study (first author, year)	Study design	*N*	Primary cognition measure	Mean age (y)	Mean MMSE	Stimulation parameters	Brain target	Sham method	Main results
Cotelli et al. (31)	Controlled study	15	Picture naming	76.6 ± 6.0	17.8 ± 3.7	20 Hz, 90% MT, 600 ms	L/R DLPFC	Coil perpendicular to the scalp	Improve action naming
Cotelli et al. (32)	Controlled study	24	Picture naming	Moderate to severe/Mild: 77.6/75.0	Moderate to severe/Mild: 14.3/19.7	20 Hz, 90% MT, 500 ms	L/R DLPFC	Coil perpendicular to the scalp	Improve action naming in mild AD and moderate-to-severe AD, but not object naming in mild AD
Cotelli et al. (33)	Double-blinded, cross-over, controlled trial	10	Auditory sentence comprehension[a]	Real-real/Placebo-real: 71.2/74.4	Real-real/Placebo-real: 16.2/16.0	20 Hz, 100% MT, 2000 stim/s for 2 weeks	L DLPFC	N/R	Improve performance with respect to baseline or placebo
Bentwich et al. (34)	Open label study	8	ADAS-cog, CGIC	74.5 ± 4.4	22.9 ± 1.7	rTMS+cognitive training(COG), 90% RMT, 10 Hz, 20 pulses x 20 trains, 2 sessions/weeks for 3 months	Six brain regions[b]	N/R	Improve ADAS-cog and CGIC after 6 weeks and 4.5 months, compared with baseline
Ahmed et al. (36)	Double-blinded, cross-over, controlled trial	45	MMSE	68.4	14.84 ± 5.5	Group 1: 20 Hz, 90% MT, 5 s, 20 trains, ITI = 25 s for 5 days; Group 2: 1 Hz, 100% MT, 2000 pulses in 2 trains, ITI = 30 s for 5 days	Bilateral DLPFC	Group 3: Coil angled away from the head	High-frequency (20 Hz) rTMS improved significantly than low-frequency (1 Hz) and sham
Rabey et al. (37)	Double-blinded, cross-over, controlled trial	15	ADAS-cog	Stim/Placebo: 72.6/75.4	Stim/Placebo:22/22	90% MT for Broca's area. L/R DLPFC 110% MT for Wernicke's area, L/R PSAC Two brain regions: 20 trains, consisting of 2 s of 10 Hz (20 pulses/train), third region: 25 trains, consisting of 2 s of 10 Hz (20 pulses/train), totaling 1,300 pulses.	Broca's area, L/R DLPFC, Wernicke's area, L/R PSAC	Sham coil	1-hour dayly rTMS-COG significantly improved ADAS-cog and CGIC than sham
Eliasova et al. (39)	Randomized, crossover, placebo-controlled study	10	Trail making test	72 ± 8	23 ± 3.56	10 Hz, 90% MT, 50 pulses x45 trains ITI = 25 s	R IFG	Vertex stimulation	High frequency rTMS significantly improved attention and psychomotor speed
Zhao et al. (38)	Randomized, double-blind, placebo-controlled trial	30	ADAS-cog, MMSE, WHO-UCLA AVLT score	70.8 ± 5.6	22.5 ± 2.7	20 Hz, MT unknown, 1 session/day and 5 days/week for total of 30 sessions	Parietal P3/P4 and posterior temporal T5/T6 according to EEG 10-20 system	Sham coil	Significantly improved ADAS-cog, MMSE and WHO-UCLA AVLT score compared with baselines, and at 6 weeks after treatment

ADAS-cog, Alzheimer Disease Assessment Scale-cognitive subsection; DLPFC, dorsolateral prefrontal cortex; IFG, inferior frontal gyrus; ITI, inter-train interval; L, left; MMSE, Mini-Mental State Examination; N/R, not reported; PSAC, parietal somatosensory association cortex; R, right; Ref, reference electrode; MT, motor threshold; rTMS, repetitive transcranial magnetic stimulation; sham, sham group; stim, stimulation group; TC, temporal cortex. WHO-UCLA AVLT, World Health Organization University of California-Los Angeles, Auditory Verbal Learning Test.

[a] *The auditory sentence comprehension subtest from the Battery for Analysis of Aphasic Deficits.*

[b] *Six brain regions: Broca's area, Wernicke's area, the right DLPFC, left DLPFC, and right and left parietal somatosensory association cortices (R-pSAC and L-pSAC, respectively).*

brain region under and around the placement, while cathode tDCS decreases (45). tDCS may modulate neuronal activity with polarity change to altering membrane polarization (46, 47). Besides, tDCS is safe (48), tolerable, and low cost for patients, therefore, the studies with tDCS use have grown in decades.

A number of small trials have suggested that tDCS may enhance specific cognitive functions in patients with AD (49–55). Ferruci and colleagues enrolled 10 patients with probable AD, who received anodal, cathodal or sham tDCS in three sessions (49). These patients underwent stimulation over the bilateral temporoparietal (TP) with a current intensity of 1.5 mA for 15 min/session. When patients underwent sham tDCS, they received stimulation for only 10 s. The authors found anodal tDCS improved word recognition task accuracy after stimulation compared with baseline (17.9 vs. 15.5,$p = 0.0068$). But cathodal tDCS significantly worsened it, while sham tDCS left it unchanged from baseline (**Table 2**).

Boggio and colleagues demonstrated that anodal tDCS over the left DLPFC and temporal cortex improved Visual Recognition Memory (VRM) in patients with AD (50). The researchers enrolled 10 AD participants who received three sessions including two real stimulations and one sham stimulation. These patients underwent real stimulation over the left DLPFC or temporal cortex with a current intensity of 2 mA for 30 min per session. The sham stimulation was applied only for the first 30 s. The authors assessed the neuropsychological tests during tDCS stimulation. They found tDCS over left DLPFC and temporal cortex significantly improved VRM tasks. The same group revised their study design, which allowed them to evaluate the long-lasting outcome of tDCS (51). They applied tDCS bilaterally over the temporal regions through two scalp anodal electrodes. These patients received stimulation over the bilateral temporal regions with a current intensity of 2 mA for 30 min a day, 5 days a week. After 5-day treatment, a significant improvement in VRM was observed, and the improvement maintained for 1 month after treatment. However, no significant improvement in visual attention or general cognitive performance was found.

In Egypt, Khedr and colleagues included 34 participants with AD and randomly assigned them to three groups. Participants of the anodal group and the cathodal group underwent daily stimulation for 10 consecutive days, with a current intensity of 2 mA for 25 min/day. The authors observed a significant improvement on MMSE scores after applying anodal or cathodal tDCS for 10 days (52).

In addition to tDCS, Cotelli and colleagues developed a combined therapy of anodal tDCS with individualized computerized memory training or motor training (55). The authors recruited 36 participants with AD and randomly assigned them to three groups. Patients in the first group underwent anode tDCS and individualized computerized memory training, while those in the second group received placebo tDCS and individualized computerized memory training. Participants in the third group underwent anodal tDCS and motor training. The tDCS stimulation was applied over the left DLPFC with a current intensity of 2 mA for 25 min a day, 5 days a week, for 2 weeks. Their findings showed a significant improvement on Face-Name associations in AD patients receiving individualized computerized memory training.

However, the results of Bystad and colleagues are inconsistent with previous findings. The authors recruited 25 AD patients and randomly assigned them into active tDCS group or placebo tDCS group. Patients underwent six sessions of stimulation over the left temporal cortex for 10 days, with a current intensity of 2 mA for 30 min/session. No significant difference was observed between the active tDCS group and placebo tDCS group in neurocognitive tests (53). To address these conflicting results, further trials are required to investigate different trial design, stimulation protocol, and standardized neuropsychological memory assessment.

Transcranial Alternating Current Stimulation

Transcranial alternating current stimulation (tACS) delivers a current which oscillates above and below zero with a given stimulation strength (i.e., peak-to-peak amplitude) at a particular frequency (56). In tDCS, the excitability thresholds of neuronal membrane potentials are modulated (44, 57), whereas tACS directly interacts with ongoing neuronal activity during cognitive or sensory-motor processes, leading to an entrainment or synchronization of brain network oscillations (56–59).

In previous studies, stimulation frequencies have been chosen within the range of the human electroencephalography frequency band and close to the frequency of the predominant oscillations of neuronal networks and cognitive processes (56, 60, 61). Brain oscillations represent various brain functions. Because specific frequencies reflect particular ongoing cognitive or sensory-motor processes (56, 60), tACS may enhance ongoing processes through exogenous augmentation of those oscillations (60, 62). Therefore, tACS has the potential to synchronize frequency-specific neuronal networks, thereby causing behavioral changes (61). Moreover, tACS may have the potential to infer causal associations between brain oscillations and cognitive processes (57, 60, 61).

Small trials have shown that tACS can improve specific cognitive functions in healthy adults by directly interacting with ongoing oscillatory cortical activity (56, 60, 61). For example, a sham-controlled crossover trial of 24 healthy adults reveled that tACS significantly improved retrieval accuracy (63). Therefore, tACS may also have potential effects on patients with AD. However, no study with tACS in AD has been published in PubMED. One trial of tACS for AD patients is registered at clinicaltrials.gov. Further trials are required to investigate the potential roles of tACS for cognitive enhancement in patients with AD.

Electroconvulsive Treatment

Cerletti et al. first used electrical stimulation to cause convulsions in a patient with schizophrenia who was experiencing delusions and hallucinations (64). They reported that they restored the patient to "clear-headedness" and health. Ever since, numerous electroconvulsive treatment (ECT) trials have been conducted for psychiatric disorders. ECT has been approved by the US FDA to treat major depression, mania, schizophrenia, and catatonia (65). Whether ECT-induced seizures can result in cognitive

TABLE 2 | Clinical trials using tDCS as a therapeutic tool in Alzheimer's disease.

Study (first author, year)	Study design	*N*	Primary cognition measure	Mean age (y)	Mean MMSE	Stimulation parameters	Brain target	Sham method	Main results
Ferrucci et al. (49)	Crossover design	10	Word recognition	75.2 ± 7.3	22.7 ± 1.8	anodal tDCS, 1.5 mA, 15 min	Bilateral temporopariatel areas, Ref: R deltoid	Stimulation was delivered for 10 s	Anodal tDCS improved accuracy of the word recognition memory task
Boggio et al. (50)	Crossover design	10	VRM	79.1 ± 8.8	17.0 ± 4.9	anodal tDCS, 2 mA, 30 min	(1) L DLPFC, (2) L TC, Ref: R supraorbital area	Stimulation was delivered for 30 s	Temporal and prefrontal tDCS improved VRM as compared with sham stimulation.
Boggio et al. (51)	Crossover design	15	VRM	71.1 ± 5.8	Anodal/Sham: 20.3/19.2	anodal tDCS, 2 mA, 30 min for 5 days	Bilateral temporal regions, Ref: R deltoid	Stimulation was delivered for 30 s	Temporal anodal tDCS for 5 days improved VRM and the improvement persists for at least 4 weeks after therapy.
Cotelli et al. (55)	Randomized, double-blind placebo-controlled	24	Face-name association task	76.6/74.7/78.2[a]	20.1/20.8/22.1[a]	anodal tDCS 2 mA, 25 min/day, 5 days/week for 2 weeks	L DLPFC, Ref: R deltoid	Stimulation was delivered for 40 s	Both Group 1 (the anodal tDCS plus individualized computerized memory training) and Group 2 (the placebo tDCS plus individualized computerized memory training) significantly improved performances at 2 weeks compared with Group 3 (the anodal tDCS plus motor training).
Khedr et al. (52)	Randomized, double-blind placebo-controlled	34	MMSE	69.7 ± 4.8	18.1 ± 3.3	(1) anodal tDCS, (2) cathodal tDCS 2 mA, 25 min/day for 10 days	L DLPFC, Ref: R supraorbital area	Stimulation was delivered for 30 s	Both anodal and cathodal tDCS improved MMSE scores compared with sham tDCS
Bystad et al. (53)	Randomized, double-blind placebo-controlled	25	CVLT-II	Active/Placebo: 70.0/75.0	20.0/21.2	anodal tDCS 2 mA, six 30-min sessions for 10 days	Left temporal cortex	Stimulation was delivered for 30 s	No significant difference between the active and placebo groups in neurocognitive tests

ADAS-cog, Alzheimer Disease Assessment Scale-cognitive subsection; atDCS, anodal transcranial direct current stimulation; ctDCS, cathodal transcranial direct current stimulation; DLPFC, dorsolateral prefrontal cortex; L, left; MMSE, Mini-Mental State Examination; min, minute; N/R, not reported; R, right; Ref, reference electrode; s, second; sham, sham group; stim, stimulation group; TC, temporal cortex; tDCS, transcranial direct current stimulation; CVLT-II California Verbal Learning Test–Second Edition; VRM, Visual recognition memory.

[a]*atDCS plus memory training group/ placebo tDCS plus memory training group/ atDCS plus motor training group.*

impairment is debated. Most adverse cognitive effects of ECT last a short amount of time. Modifications of and improvements to treatment techniques have been implemented to minimize cognitive side effects (66).

Numerous studies and many meta-analyses have shown gray matter atrophy and lower levels of brain-derived neurotrophic factor (BDNF) are associated with AD (1, 2). Moreover, a meta-analysis revealed that ECT may increase BDNF levels in depressed patients (67). Studies have investigated APOE-ε4 and beta amyloid level after ECT treatment, but the findings are contradictory (68). Moreover, in a trial of ECT for depression, gray matter, and hippocampus volume were reported to increase following ECT (69).

Kumar et al. reviewed 5,154 publications and suggested ECT may improve long-term cognitive outcomes in late-life depression (LLD) (70). For example, Hausner et al. included 44 elderly inpatients with MDD, and divided these patients into three groups (dementia group: 12 subjects, MCI group: 19 subjects, no cognitive impairment (NCI) group: 13 subjects) (71). They delivered right unilaterally at minimal 250% seizure threshold or bilaterally at minimal 150% seizure threshold, two to three times per week. In the dementia group, the pre-ECT MMSE = 22.7 (4.4) and the post-6 month MMSE is 25.6 (3.0). Verwijk et al. included 42 depressed patients aged ≥55 years (72). They found improvement in the Trail Making Test-A (76.21 vs. 61.63, $p = 0.024$) and Letter Fluency Test (9.00 vs. 12.50, $p = 0.004$) but not in the MMSE after 6 months. Besides, a retrospective cohort study of 126 patients with ECT treatment reported that the MMSE score was significantly higher at the 6-month compared with baseline (27.96 vs. 26.25, $p < 0.01$) (73). However, these studies addressed elderly depression instead of AD. One trial of ECT for AD patients has been registered at clinicaltrials.gov. Further studies of ECT in patients with AD are required.

Magnetic Seizure Therapy

Magnetic seizure therapy (MST) is a new implementation of TMS. It is based on the rationale of ECT. Similar to ECT, MST induces seizures using high-intensity rTMS, but with greater control. One study demonstrated the antidepressant effect of MST and identified a response rate of approximately 50–60% (74). A study of 10 patients with refractory depression reported that the relative glucose metabolism increased in brain regions including the medial frontal cortex, orbitofrontal cortex, basal ganglia, and DLPFC after MST treatment (75). This indicated that the mechanism of MST treatment may be associated with these activities in these brain regions.

A systematic review of 11 MST trials revealed little to no adverse cognitive effects (76). Moreover, Kosel et al. identified significantly-improved verbal learning performance in refractory depressed patients (77). Besides, Lisanby et al. found that MST improved the velocity and accuracy of visual cancellation tasks in patients with major depression (78). These studies have revealed that TMS may improve cognitive function in depressed patients. However, until now no trial with MST in AD has been published in PubMED or registered at clinicaltrials.gov. Luber et al. reviewed the applications of TMS and MST in neuropsychiatric illnesses related to cerebral aging (79). The authors suggested MST may enhance cognition or reduce amnesia. Therefore, MST warrants further exploration for its potential effect on patients with AD.

Cranial Electrotherapy Stimulation

Cranial Electrotherapy Stimulation (also referred to as cranial electrostimulation [CES]) applies pulsed, low-amplitude, electrical currents (typically <1 mA) to the brain through ear clip electrodes. The US FDA has approved CES for the treating depression, anxiety, and insomnia (80).

Small trials have demonstrated that transcutaneous electrical nerve stimulation (TENS) may enhance specific cognitive function in patients with AD (81, 82). Scherder and colleagues (81) recruited 16 participants with early-stage AD, and assigned them equally into the experimental group or the placebo group. The researchers fixed two electrodes on the participant's back between Th 1 and Th 5. These patients underwent stimulation with asymmetric biphasic square impulses in bursts of trains, 30 min per day, for 6 weeks. Each trains contained nine pulses with an internal frequency of 160 Hz. The repletion rate was 2 Hz and pulse width was 40 μs. After a 6-week treatment, a significant improvement was observed in Face Recognition, Picture Recognition and Recognition subtest of the 8 Words Test.

Based on these promising findings, the same research team from the Netherlands used the same protocol in the mid-stage of AD (82). They enrolled 16 patients with mid-stage AD. The subjects of the experimental group received 30-min stimulation daily for 6 weeks. The protocol was similar to previous study. Compared with TENS in an early stage, they observed TENS caused less beneficial effects in patients in the mid-stages of AD.

Scherder and colleagues further investigated the cognitive effects of CES in AD patients, because CES mimics TENS but mediated stimulation via the patients' earlobes (head) instead of patients' back. This research team selected 18 participants with AD, and randomly assigned them into the intervention group and the control group (83). Participants of the intervention group underwent low-frequency (0.5 Hz) stimulation with an intensity of 10 to 600 μA, 30 min per day, 5 days per week for 6 weeks. However, after 6-week CES treatment, no improvement in cognition was found.

Therefore, Scherder and colleagues launched a study of high-frequency (100 Hz) CES in 21 patients with AD, and assigned theses participants into the experimental group or the control group (84). The protocol was similar to previous trial except the frequency. Patients in the intervention group underwent high-frequency (100 Hz) stimulation with an intensity of 10–600 μA, 30 min/day, and 5 days/week. However, the results revealed no cognitive improvement after 6-week treatment. Further research with large sample sizes and better designs may be required to evaluate the effect of CES on cognition.

Non-invasive Vagus Nerve Stimulation

Non-invasive VNS (nVNS) does not require a surgical procedure to implant an electrode. nVNS devices are portable and can stimulate the vagus nerve indirectly through the skin of neck or

ear (85–87). nVNS is less expensive, carries a lower risk, and is more convenient than iVNS.

Two small trials have shown iVNS may enhance cognitive function in patients with AD (21, 22). In Sweden, researchers enrolled 10 patients with AD (22). Each patient received surgery to implant a pulse generator, which deliver programmable signals to the left-side tenth cranial nerve. The initial settings were frequency 20 Hz, pulse width 500 μs, and current 0.25 mA. The stimulation was on for 30 s followed by a pause for 5 min. After 3 months of treatment, they found the response rates were 70% (seven of 10 patients) on the ADAS-Cog and 90% (nine of 10 patients) on the MMSE. Moreover, 6 months after the iVNS treatment, response rate was still 70% on the ADAS-Cog, and 70% on the MMSE. Adverse effects of invasive VNS were transient and mild.

Therefore, based on these promising findings, the same research team recruited another seven patients with AD. The researchers followed up these total 17 patients for at least 1 year (21). They found that 1 year after iVNS treatment, the score of the ADAS-Cog in seven patients did not decline or even increase, while the score of the MMSE in 12 patients did not decline or even improve compared with baseline. These two small trials revealed that invasive VNS was well-tolerated and improved specific cognitive functions in MMSE and ADAS-Cog after 1 year and 3 months of treatment, respectively.

Non-invasive VNS may affect cognition through the same neural pathway. Until now, no trial with non-invasive NVS in AD has been published in PubMED or registered at clinicaltrials.gov. Further studies of non-invasive VNS in patients with AD are required.

BRAIN TARGETS AND MECHANISMS IN INVASIVE BRAIN STIMULATION

Nucleus Basalis of Meynert

Nucleus basalis of Meynert (NBM) is the first target for DBS in AD (11). The NBM is a group of cholinergic nucleus in the forebrain (88). Previous studies have shown loss of central cholinergic neurons of the basal forebrain cholinergic system in AD patients (89–91). Moreover, in early-stage AD, volume reductions developed in posterior parts of NBM (92). The atrophy of cholinergic neurons is considered to result in cognitive impairment in AD (93). Therefore, current DBS trials are based on the hypothesis that stimulating NBM may enhance the cholinergic system and thereafter improve the cognitive functions in patients with AD (94).

Fornix

The fornix is an integral white matter bundle in the medial diencephalon. It connects the medial temporal lobes to the hypothalamus, and serves as a vital role in the memory circuit of Papez (95, 96). Previous studies have shown that fornix lesions cause severe memory impairments (97, 98). Besides, the memory impairment and progression in AD are correlated with axonal degeneration and dysfunction in the fornix (99). Therefore, several trials were performed to evaluate the hypothesis that fornix DBS could enhance the circuit of Papez and thereafter improve memory and cognitive functions (10, 16).

Vagus Nerve

The possible mechanism for cognitive improvement through iVNS is based on the neural anatomy. The vagus nerve (tenth cranial nerve) projects to the locus coeruleus (LC), which is the major nucleus of origin for noradrenergic projections in the brain (100). Studies have revealed atrophy of the LC in patients with AD (101). Moreover, decreased norepinephrine (NE) concentration in the temporal cortex is correlated with cognitive impairment in patients with AD (102). In addition, NE can inhibit the inflammatory activation of microglial cells and functions as an endogenous anti-inflammatory agent (103). Therefore, iVNS may increase the NE concentration and decrease inflammation. These mechanisms may involve in specific cognitive functions in AD. Further trials with large sample are required to investigate this hypothesis.

BRAIN TARGETS AND MECHANISMS IN NON-INVASIVE BRAIN STIMULATION

Dorsolateral Prefrontal Cortex (DLFPC)

In contrast to IBS, no consensus has been made for NIBS regarding which brain region should be targeted in AD. Most NIBS studies (31–33, 36, 52, 55) including TMS, tDCS targeted the DLPFC, a region involving in the decline of working memory and specific executive functions in early AD (104, 105). Moreover, the DLPFC may enable compensatory mechanism for working memory performance, and change dynamic neuroplasticity after prefrontal cortex damage (106–108). Thus, these findings may support the use of DLPFC as a potential stimulation target to improve specific cognitive functions in patients with AD.

Broca's Area, Wernicke's Area, and Parietal Somatosensory Association Cortex (PSAC)

In addition to DLPFC, other cortex areas have been investigated. Broca's area, located in the left frontal part of the temporal lobe, involves sentence comprehension in articulatory rehearsal (109) whereas Wernicke's area, located in the left frontal and left posterior part of the temporal lobe, processes lexical meanings of words (110). Right parietal somatosensory association cortex (PSAC) is in the parietal lobe and associated with visual and spatial attention impairment in AD (111, 112). Two trials targeted six brain regions including right DLPFC, left DLPFC, Borca's area, Wernicke's area, PSAC, and left PSAC (34, 37). These two trials of rTMS over DLPFC, Broca's area, Wernicke's area, and PSAC reported improved ADAS-cog in patients with AD.

Inferior Frontal Gyrus

Right inferior frontal gyrus (IFG) plays an important role in the right-lateralized ventral attention network governing reflexive reorienting (113, 114). Previous neuroimaging study has demonstrated that right IFG involves in dissociating inhibition, attention, and response control in the frontoparietal network (115). The lateral prefrontal cortex, particularly the right IFG,

can be activated during response inhibition in the go/no-go task (116). Chambers and colleagues reported that rTMS over the right IFG could modulate stop-signal reaction time (117). Elisaova and his colleagues targeted IFG and found that rTMS may improve attention in patients with early AD (39).

Temporal Cortex

Increasing evidences have shown the association between dysfunction or atrophy of temporal cortex and Alzheimer's diseases (118). Mesial temporal lobe dysfunction is correlated with memory deficits such as episodic memory impairment (119). Boggio and colleagues reported that anodal tDCS over bilateral temporal cortex improved visual recognition memory in patients with AD (51). However, Bystad and colleagues found no significant improvement after tDCS over left temporal cortex (53). The inconsistence may be caused by anatomical differences, limited sample size, severity of AD, and different neuropsychological tests (53). Further studies are suggested to evaluate these differences.

Temporopariatel Cortex

In addition to temporal cortex, hypofunction or atrophy of temporopariatel (TP) cortex has been noted in AD (120, 121). Both pilot trials of rTMS and tDCS over TP areas have shown promising results. Zhao and colleagues applied rTMS over TP cortex and found a significant improvement in cognitive and language function (38). Ferrucci and colleagues reported that tDCS over TP areas can improve recognition memory performance in patients with AD (49).

In summary, current invasive DBS studies aimed at the subcortical areas such as NBM and fornix, while non-invasive DBS studies aimed the cortical areas such as DLFPC, temporal cortex, Broca's are, Wernicke's area, and PSAC. Generally speaking, the subcortical area is associated with emotion and behavior (122), whereas cortical function is related to cognition (123). However, whether the stimulated regions meet the outcome variables are not clearly evaluated and understood. Further studies are needed to evaluate the targeted brain areas and cognitive outcomes.

Stimulation Therapy Combined With Cognitive Training or Cognitive-Challenging Activities

Two trials of rTMS combined with cognitive training (rTMS-COG) have shown promising results in patients with AD (34, 37) and suggest synergistic effects better than rTMS therapy or cognitive training alone. However, the synergistic effects of rTMS-COG are unclear due to the lack of a control group with cognitive therapy only. Therefore, this made it difficult to differentiate the effects between rTMS and cognitive therapy. Furthermore, they applied rTMS over six brain areas including DLPFC. This also made it difficult to compare with other rTMS trials over one or two brain areas. Further controlled-design, larger, multi-center studies are needed.

Practical and Ethical Challenges

IBS treatments, especially DBS, need surgical procedures and cause more concerns about the safety and ethical issues. A few pilot studies have reported that the surgery was well-tolerated with no adverse effects (10, 16, 124), but an AD trial with DBS over fornix has noted four acute serious safety events and three long-term serious events (15). Because DBS surgery and stimulation may cause neurologic and psychiatric side effects, and patients with AD tend to have more comorbidities than normal aged population, several reviews have raised the ethical considerations about participants selection, decision-making procedure, and informed consent (124, 125).

On the other hand, NIBS therapies such as rTMS and tDCS led to less safety and ethical concerns. rTMS may cause mild headache, tinnitus, short-term hearing loss, short-term memory change, or acute psychiatric effects. All these adverse effects are transient and disappear after turning off (25). The most serious side effect is seizure, but the incidence is rare. In a study that reviewed trials by rTMS over non-motor areas between 1998 and 2003, only two seizure cases were found in total 3,092 participants (126). Similarly, tDCS may cause relatively minor adverse effects including fatigue, mild headache, nausea, or itching (127, 128).

Improving Cognition Indirectly by Improving Depression

Previous studies of ECT and MST in depressed patients have shown improvement not only in depressive symptoms but also in cognitive functions (71, 72, 77, 78). However, those trials investigated older participants with depression instead of participants with AD. Therefore, the improvement in cognition may correlate with the improvement in depressive symptoms. Whether ECT or MST can improve cognition directly or indirectly remains unclear. Further studies are needed to explore the underlying indirect mechanisms in AD.

CONCLUSIONS

Studies are increasingly investigating brain stimulation techniques as novel therapeutic approaches to AD. Although some studies have revealed promising results, many lack large samples and the appropriate power, or are poorly designed and not hypothesis-driven. This review examined IBS therapies, namely DBS and invasive VNS, and NIBS therapies, namely TMS, tDCS, tACS, ECT, MST, CES, and non-invasive VNS. Because many brain stimulation methods have no standard settings and guidelines, a robust comparison of these trials remains incomplete. However, stimulation-associated improvements in memory and specific cognitive functions are promising. Moreover, stimulation that is targeted at multiple brain regions or combined with other treatments such as cognitive training appear to produce more positive effects. Therefore, although the field of brain stimulation is relatively immature, such techniques, especially rTMS, warrant further study for their therapeutic implications on patients with AD.

AUTHOR CONTRIBUTIONS

C-HC drafted the initial manuscript. H-YL provided expert opinions and reviewed the final submitted manuscript. C-HL critically reviewed the draft of manuscript, and approved the final submitted version manuscript.

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Acoustic Hyper-Reactivity and Negatively Skewed Locomotor Activity in Children With Autism Spectrum Disorders: An Exploratory Study

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Investigation of objective and quantitative behavioral phenotypes along with neurobiological endophenotypes might lead to increased knowledge of the mechanisms that underlie autism spectrum disorders (ASD). Here, we investigated the association between locomotor dynamics and characteristics of the acoustic startle response (ASR) and its modulation in ASD ($n = 14$) and typically developing (TD, $n = 13$) children. The ASR was recorded in response to acoustic stimuli in increments of 10 dB (65–105 dB SPL). We calculated the average ASR magnitude for each stimulus intensity and peak-ASR latency. Locomotor activity was continuously measured with a watch-type actigraph. We examined statistics of locomotor activity, such as mean activity levels and the skewness of activity. Children with ASD had a significantly greater ASR magnitude in response to a weak acoustic stimulus, which reflects acoustic hyper-reactivity. The skewness of all-day activity was significantly more negative in children with ASD than those with TD. Skewness of daytime activity was also more negative, although only of borderline statistical significance. For all children, the higher mean and more negatively skewed daytime activity, reflecting hyperactivity that was associated with sporadic large daytime "troughs," was significantly correlated with acoustic hyper-reactivity. The more negatively skewed locomotor activity occurring in the daytime was also associated with impaired sensorimotor gating, examined as prepulse inhibition at a prepulse intensity of 70 dB. This comprehensive investigation of locomotor dynamics and the ASR extends our understanding of the neurophysiology that underlies ASD.

Keywords: acoustic hyper-reactivity, acoustic startle reflex, autism spectrum disorders, endophenotypes, locomotor activity, prepulse inhibition, sensorimotor gating

INTRODUCTION

Expectations of translational research in relation to being able to determine the biological pathology and fully effective treatments for autism spectrum disorder (ASD), are increasing. Specifically, the expectation of acquiring a deeper understanding of objective and quantitative behavioral and neurobiological indices is growing. Such indices will contribute to the progress of basic and clinical research and lead to the identification of promising ASD phenotypes or endophenotypes.

One promising objective and quantitative endophenotype for translational research is the acoustic startle response (ASR) and the way it is modulated, including aspects such as habituation and prepulse inhibition (PPI). The neurophysiological indices of ASR are often used to assess information processing differences across (ethnic) groups and species as they can be evaluated by using similar nonverbal experimental designs (1, 2). Sensory abnormalities often occur in people that have ASD (3, 4) and are regarded as important elements in this disorder. Among the ASR indices, an increased ASR magnitude to weak stimuli might act as a useful indicator for translational research, especially when considering acoustic hyper-reactivity. For example, recent research (5, 6) has indicated that in response to weak stimuli, peak-ASR latency is prolonged and ASR magnitude is greater in ASD children when compared to those with typical development (TD). Importantly, the difference in these indices which were associated with emotional/behavioral difficulties in ASD children (6), exhibited a fair to moderate degree of stability over a follow-up period of 1 year (7).

Another promising candidate index for translational research is locomotor dynamics. Locomotor activity is a behavioral index that has been examined in both basic (animal) and clinical research in relation to psychiatric and developmental disorders (8–12). In terms of ASD, locomotor activity is frequently examined using an actigraph, primarily to document atypical sleep patterns (13–17). However, statistical measures of daytime, waking locomotor activity have not been well established in ASD. This is an important oversight, especially as recent studies of depression (18, 19) and attention-deficit hyperactivity disorder (20–22) have highlighted the usefulness of measures such as mean locomotor activity during waking periods. Compared with the ASR, measuring locomotor activity with an actigraph or by video-recording can be less invasive and more continuous, even during infancy (23). Thus, identifying the clinical significance of locomotor activity during early development might help uncover fundamental mechanisms in the psychopathology of ASD.

Thus, this study's aim was to examine the association between locomotor activity and ASR indices in children with ASD. Locomotor activity was recorded by actigraph and analyzed. We examined several ASR properties, including the magnitude of the ASR to sounds of varying intensities, peak-ASR latency, habituation, and PPI. Our hypothesis was that acoustic hyper-reactivity (a greater ASR magnitude to weak stimuli)—which is related to ASD—would also be related to the dynamic properties of locomotor activity measured in daily life.

MATERIALS AND METHODS

Participants

Fourteen Japanese children with ASD (13 boys) and 13 with TD (10 boys) participated in the study (age: 7–16 years). Participants were recruited through locally placed advertisements. Experienced child psychiatrists assigned diagnoses after reviewing the children's medical records and performing a clinical interview based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (24). The Autism Diagnostic Interview-Revised (25) and the Autism Diagnostic Observation Schedule (26) were used to confirm diagnoses. Neither sex, age (age in months; ASD 125.6 ± 30.9; TD 138.5 ± 38.2; $U = 76$, $p = 0.467$), or the estimated intelligence quotient (IQ: ASD 105.7 ± 23.3; TD 104.7 ± 18.3; $U = 31$, $p = 0.958$) differed significantly between the two groups. Additionally, when using the Wechsler Intelligence Scale for Children-Third Revision (27) the estimated IQ of every child in the study was above 70. None of the children were smokers or were currently being medicated with psychotropic substances. In addition, none of them had any degree of hearing loss according to the results from the annual school health check-up which includes bilateral hearing screening of 1,000 Hz acoustic stimuli larger than 30 dB and 4,000 Hz acoustic stimuli larger than 40 dB. Further, none of the children had any abnormalities of the central nervous system apart from autism. Exclusion criteria for the TD group included having a previous or current psychiatric diagnosis or learning disability.

Ethical Approval and Informed Consent

This study was undertaken in accordance with the principles laid out in the 1964 Helsinki Declaration and its subsequent amendments and institutional review-board approval was granted by the Research Ethics Committee of the National Center of Neurology and Psychiatry (#A2013-112) and the research ethics committee of the Graduate School of Education, the University of Tokyo (#13-119). Before being accepted into the study, the study procedures were explained in detail and written informed consent was obtained from each participant and their parents.

Startle Response

Details of the stimulus-presentation and eyeblink-acquisition methodology have been presented previously (5, 6, 28, 29). The startle paradigm that was used to test participants comprised three blocks, and we examined the following ASR measures: (i) average eyeblink magnitude in response to each of the five pulse intensities (65, 75, 85, 95, and 105 dB SPL) in block 1; (ii) average peak-ASR latency; (iii) ASR habituation during each test period, calculated as the reduction in the ASR magnitude percentage (at 105 dB SPL) between the first and third blocks; (iv) PPI at prepulse intensities of 65, 70, and 75 dB SPL. Regarding prepulse intensity, each PPI was calculated as the percentage reduction in the ASR magnitude in block 2 between the pulse alone and the pulse with prepulse trials. As the brain mechanisms subserving PPI do not become sufficiently mature until children become 8–10 years old (30–32), we did not examine ASR measures in

four boys (two with ASD and two with TD) who were less than eight years old. In addition, because one boy with ASD could not tolerate the startle stimulus, he did not finish the session and his data were therefore not used in the subsequent statistical analysis.

Assessment of Locomotor Dynamics

All participants were instructed to wear the MicroMini Motionlogger actigraph (Ambulatory Monitors Inc., Ardsley, NY, USA) (33) on the wrist of their non-dominant hand for more than seven days during school vacations in spring, summer, or winter (TD: 7.7 ± 1.9 days, ASD: 7.8 ± 1.8 days, $U = 80$, $p = 0.574$). Children were expected to wear this device throughout the study period, except for when bathing, or during rigorous exercise, or when undertaking any other activity that might cause damage to the device, and to lead their lives normally during the period of actigraphic recordings.

This particular actigraph has been used extensively in clinical research (8, 33–35). Locomotor activity was assessed with a uni-axial piezo-electronic accelerometer sensor that is able to detect even minor differences in body acceleration (≥0.01 G/rad/s). In the current study, we used zero-crossing counts that were collected together for each 1-min epoch as a measure of locomotor activity. After children returned the actigraph, ActMe software (ver. 3.10.0.3, Ambulatory Monitoring Inc., Ardsley, NY, USA) was used to download their activity data. Any locomotor activity data that were collected when participants were not actually wearing the device were not included in the analysis. This was done using Action W-2 software (ver. 2.4.20, Ambulatory Monitoring Inc., Ardsley, NY, USA) to manually label the bad time periods (bins) when the participants had taken off the device.

Sleep–wake cycles were scored and sleep measures were also analyzed using Action W-2 software. Sleep epochs were determined based on the Cole-Kripke algorithm (36). One boy with ASD and two TD girls and two TD boys were excluded from the actigraph behavioral data analysis because they did not wear the actigraph for a sufficient period of time during the daytime.

Sleep measures obtained through actigraphy were (a) sleep duration: the total sleep time in minutes between the time of sleep-onset and waking time; (b) sleep latency: the total time in minutes between going to bed and sleep onset; (c) wake-after-sleep onset (WASO): the number of minutes spent awake during the night after the onset of sleep; and (d) sleep efficiency: the ratio between the total sleep time and amount of time spent in bed at night. Actigraphic sleep parameters were calculated each night for each participant and then averaged for each participant.

We also calculated the mean, standard deviation, skewness, and kurtosis of locomotor activity as these can demonstrate behavioral alterations associated with psychiatric disorders or psychological states (10, 19). For example, higher or lower than normal mean activity levels can characterize states related to psychomotor retardation or agitation, respectively. A right-skewed distribution indicates the presence of extreme values higher than their mean ("occasional bursts"). Right-skewed activity levels with a low mean can characterize the increased intermittent patterns of locomotor activity that are exhibited by patients with major depressive disorder (19). Further, this pattern of locomotor activity has been significantly associated with the worsening of depressive mood in healthy adults and depressive patients (10, 19). Therefore, we evaluated the association between these statistics and the ASR indices. As no significant differences between groups were detected in the standard deviation or kurtosis of locomotor activity, detailed results for these statistics are not reported in the text.

Statistical Analysis

Chi-square tests (and when necessary Fisher's exact tests) were used to examine categorical aspects of the participants' demographic data. As most of the variables relating to ASR and locomotor activity were not normally distributed, nonparametric analyses were performed. Specifically, differences in mean parameter values were examined with the Mann-Whitney *U*-test. Associations between the variables were computed with Spearman's rank order correlation coefficients. As some children were excluded from the ASR and/or actigraph behavioral data analysis, data from 10 children (1 girl) with ASD and 8 children (1 girl) with TD were included in the analysis of the relationship between ASR measures and locomotor activity statistics, while data from 11 children (1 girl) with ASD and 11 (3 girls) with TD were included in the analysis of the relationship between ASR measures and sleep measures. A Bonferroni adjustment for multiple comparisons was used to correct significance levels. Statistical significance was set at $p < 0.05$. All analyses were conducted with SPSS Version 22 (IBM Japan, Tokyo, Japan).

RESULTS

Startle Measure Differences Between ASD and Control Children

Startle measures are presented in **Table 1**. Children with ASD had significantly prolonged peak-ASR latencies. Additionally, their ASR magnitude was also significantly greater at the 65-, 75-, and 95-dB stimulus intensities. A trend toward a greater ASR magnitude was also observed in ASD children at the 85-dB stimulus intensity. For PPI, the only significant difference between groups was for the prepulse intensity of 65-dB. Statistically significant differences in habituation or PPI were not observed between the groups at any of the other prepulse intensities.

Differences in Locomotor Dynamics Between Children With Autism Spectrum Disorders and Controls

Locomotor activity is presented in **Table 2**. Significantly more negative skewness—defined as a left-skewed distribution (or a long left tail relative to the right tail) with extreme values lower than their mean—was observed for all-day activity in children with ASD, indicating an increase in sporadic large "troughs" below mean activity levels. The skewness of daytime activity was also more negative in those with ASD, although it was only of borderline statistical significance. No other significant differences in locomotor activity or any differences in sleep measures were observed between the groups.

TABLE 1 | Acoustic startle response measures.

	Typical development		Autism spectrum disorders			
	Mean	***SD***	**Mean**	***SD***	***U***	***p***
Peak Startle Latency (ms)	66.0	11.7	90.4	17.3	19	0.006
ACOUSTIC STARTLE RESPONSE (MICROVOLTS)						
65 dB	33.6	20.9	53.6	27.1	25	0.020
75 dB	27.8	11.6	47.9	25.0	28	0.033
85 dB	32.6	7.7	61.4	46.6	31	0.052
95 dB	38.1	18.5	66.5	57.5	23	0.014
105 dB	55.2	37.3	85.6	71.4	43	0.250
Habituation (%)	29.3	7.3	22.4	18.7	24	0.248
PREPULSE INHIBITION (%)						
65 dB prepulse	35.6	20.2	14.1	13.4	17.5	0.008
70 dB prepulse	32.1	19.8	22.0	19.4	40	0.290
75 dB prepulse	33.0	19.3	33.6	21.5	59	0.922

SD, Standard deviation; Mann-Whitney U-test. Number of participants (Typical Development: Autism Spectrum Disorders) for Peak startle latency = 11:11; Acoustic startle magnitude (65 dB) = 11:11; (75 dB) = 11:11; (85 dB) = 11:11; (95 dB) = 11:11; (105 dB) = 11:11; (Habituation) = 9:8; Prepulse inhibition (65-dB prepulse) 10:11; (70-dB prepulse) 10:11; (75-dB prepulse) 11:11.

TABLE 2 | Locomotor dynamics.

	Typical development		Autism spectrum disorders			
	Mean	***SD***	**Mean**	***SD***	***U***	***p***
SLEEP MEASURES						
Sleep duration (minutes)	517.7	64.2	516.2	39.4	87	0.846
Sleep latency (minutes)	7.8	3.6	7.9	3.3	87	0.846
Wake after sleep onset (minutes)	28.8	20.5	32.4	24.5	84	0.734
Sleep efficiency (%)	94.5	3.9	93.8	4.6	87	0.846
LOCOMOTOR ACTIVITY STATISTICS ALL DAY ACTIVITY						
Mean	147.9	18.9	159.0	7.5	35	0.117
Skewness	0.0	0.2	−0.2	0.2	28	0.042
DAYTIME ACTIVITY						
Mean	231.7	32.0	239.5	18.4	41	0.243
Skewness	−1.1	0.6	−1.6	0.5	31	0.066

SD, Standard deviation; Mann-Whitney U test. Number of participants (Typical Development: Autism Spectrum Disorders) for Sleep measures = 13:14; Locomotor activity statistics = 9:13.

Relationship Between Locomotor Dynamics and Startle Measures

When all the children were combined, mean activity levels for daytime activity were significantly correlated with ASR magnitude for the 75-dB stimulus (rho = 0.484, $p = 0.042$). Likewise, activity-skewness values for daytime activity were significantly correlated with ASR magnitude for the 65-dB stimulus (rho = −0.626, $p = 0.005$), 85-dB stimulus (rho = −0.499, $p = 0.035$), and PPI at 70-dB prepulse intensity (rho = 0.566, $p = 0.018$). The negative skewness of daytime activity was significantly correlated with the ASR magnitude to a 65-dB stimulus even after a Bonferroni correction for multiple comparisons was applied. No other significant correlations were observed between locomotor activity or any sleep parameter and the ASR measures.

These relations were also confirmed within each group because ASR magnitude for the 65-, 75-, and 85-dB stimuli was either significantly different or tended to differ between diagnoses. This analysis revealed a statistically significant correlation between daytime skewness and ASR magnitude for the 65-dB stimulus (rho = 0.745, $p = 0.013$) in the ASD group.

DISCUSSION

This study investigated locomotor activity that was measured by actigraph in ASD and TD children. We also investigated the ASR, its modulation by PPI and habituation, and how these indices were related to locomotor dynamics. Results indicated that locomotor activity skewness for children with ASD was significantly more negative for all-day activity, and tended to be more negative for daytime activity. When all children were combined, the mean and skewness values for daytime locomotor activity correlated with several ASR measures, including ASR magnitude for 85 dB stimuli or weaker and PPI at a 70-dB

prepulse intensity. Additionally, in the ASD group, as the ASR magnitude to a weak 65-dB stimulus increased, the skewness values for daytime activity became more negative. Our results thus suggest that atypical hyperactivity behavior observed in locomotor dynamics might be caused, in part, by acoustic hyper-reactivity to weak acoustic stimuli.

To our knowledge, this study is the first to report a relation between locomotor dynamics and ASR indices in humans. The skewness of all-day locomotor activity was more negative in ASD than in TD children. These results suggest that negatively skewed all-day activity might serve as a promising quantitative behavioral index related to ASD.

Higher mean activity levels and more negatively skewed values for daytime locomotor activity characterize behavior in children as being hyperactive with sporadic large "troughs" in daytime activity. In the current study, these values were significantly linked to an increased ASR magnitude to weak 65-dB stimuli, a characteristic which has been associated with several autistic traits in ASD and TD children (5, 6). Our finding that the daytime skewness in locomotor activity tended to be more negative in those with ASD is consistent with the idea that the prevalence of attention-deficit hyperactivity disorder in ASD is high (37). However, hyperactivity/inattention might be associated with acoustic hyper-reactivity. Thus, the analysis of daytime locomotor activity, especially daytime skewness, might provide promising behavioral phenotypes that are related to clinical features in ASD, such as acoustic hyper-reactivity or hyperactivity/inattention.

Our results support the utility of focusing on third-order statistical moments such as skewness in addition to standard descriptive statistics when characterizing behavioral alterations in ASD children. In a recent study, children with ASD were found to be more active during rest periods than healthy children, although this difference was non-significant in statistical terms. However, in rest periods the kurtosis and skewness of their activity distributions were significantly smaller than those of healthy children (38). Other recent research (18, 19) that investigated the relationship between locomotor dynamics and depressive mood reported that the worsening of depressive mood was linked to a greater intermittency of locomotor activity, as seen in lower mean scores and increased positive skewness values. As higher order statistics successfully capture intermittency or non-Gaussian distributions in natural phenomena, these types of analyses should be useful in assessing the locomotor dynamics of children with ASD. Thus, further investigation of daytime and sleep activity using these higher order statistics might reveal more apparent characteristic behavioral alterations in ASD and other psychiatric disorders.

In this study, ASR measures were related to several aspects of locomotor dynamics, which suggests that basic and clinical research using ASR measures and locomotor dynamics might facilitate a better understanding of the association between ASD and co-occurring psychiatric or developmental conditions. For example, numerous animal studies (although not evaluating skewness of locomotor activity) have reported a relationship between increased locomotor activity and decreased PPI in connection with dysfunction in dopaminergic, serotonergic, and glutamatergic neurotransmitter regulation (39–43). These associations are thought to be related to hippocampal function (40, 43), which suggests an underlying shared biological mechanism between some aspects of locomotor activity and the ASR. We found that for the daytime activity of both groups combined, more negative skewness was significantly associated with smaller PPI at the prepulse intensity of 70 dB, which has been related to some subcategories of autistic traits and with emotional/behavioral difficulties in children with ASD and TD in previous studies (5, 6). In the current study, the skewness of all-day locomotor activity was significantly more negative, and the skewness of daytime locomotor activity more negative (although only of borderline significance) in ASD children, suggesting that a comprehensive investigation of locomotor activity and its relationship with ASR modulation might help clarify the neurophysiological basis of ASD and other clinical problems in children. Additionally, assessing locomotor activity, especially skewness, in daily settings might also serve as a preliminary test to predict ASR indices, including PPI. As locomotor activity can be examined less invasively and more continuously than the ASR even in infancy (23), its evaluation during early development in relation to ASD symptom severity might provide an insight into the fundamental mechanisms that contribute to the broad vulnerability to developmental psychopathology seen in ASD.

The fact that both the ASD and TD groups contained few participants is a major limitation of this study. Even though we were able to identify significantly more negative skewness in the all-day locomotor activity in those with ASD, and significant associations between some aspects of locomotor dynamics and ASR indices, the sample size might nevertheless have been too small to detect other significant differences or associations. For example, the significant relationship between PPI and mean locomotor activity, which has been reported in previous animal studies (39–43), was not observed in this study. In particular, no significant differences were found for the sleep measures despite reports of such differences in previous studies (13–17). This might be related to the small number of children included in this study. Similar sleep problems are experienced at a markedly higher prevalence in school-aged children with ASD (44–83%) than in those with TD, and, atypical sleep patterns, such as prolonged sleep latency (14–17), lower sleep efficacy (14, 16, 17), and longer WASO (13, 14) are frequently reported in children with ASD. However, a previous study (44) reported that although school-age children with Asperger syndrome or high-functioning autism had longer sleep latency and lower sleep efficiency on school days, these differences were not found over the weekend (44), suggesting that sleep patterns in ASD might differ according to the level of daytime activity, and that children with ASD might have difficulty in regulating their school-life rhythm. Thus, the fact that no significant differences were observed in the sleep measures between the ASD and TD groups in this study might be partly due to the locomotor data acquisition period, which was during long seasonal school vacations when participants did not have to adjust to the rhythms of school life. Participants with ASD might exhibit more sleep problems during school days. Future studies with larger samples that include data from both

seasonal school vacations and school days are necessary to clarify the relationship of sleep measures to ASR measures.

Additionally, this study only included ASD children without intellectual disabilities and IQ-matched controls, who were mainly boys, while the age span, which might be important for differences in hormone levels, was rather large. By using intellectual disabilities as an exclusion criterion, we aimed to avoid the high rates of participant rejection reported previously (45). However, it is possible that the ASR profile of ASD children with intellectual disabilities might also differ. Moreover, although not much is known about gender differences in the locomotor dynamics of children, sexual hormones are known to have an effect on ASR modulation, such as PPI (1, 2). Thus, future research needs to use larger samples to examine these associations in participants with intellectual disabilities and in both sexes while ensuring that there is a narrower age range.

CONCLUSION

The results from the current study suggest that negatively skewed all-day locomotor activity might serve as a promising quantitative behavioral index related to ASD. For all children, acoustic hyper-reactivity (assessed as a greater ASR magnitude in response to weak stimuli) was related to higher levels of locomotor activity and a negatively skewed activity distribution (which reflected hyperactivity that was characterized by large sporadic "troughs," during the daytime). The more negatively skewed daytime locomotor activity was also associated with impaired sensorimotor gating (i.e., PPI). This comprehensive investigation of locomotor dynamics and the ASR thus extends our understanding of the neurophysiology that underlies ASD.

AUTHOR CONTRIBUTIONS

HT, ToN, JK, HK, KY, TA, YY, and YK conceived and designed the experiments. HT, ToN, YY, and YK supervised the project. HT and YK confirmed diagnoses. HT, ToN, JK, and TaN performed the experiments. HT, ToN, JK, YY, and YK analyzed the data. HT, ToN, JK, MI, KE, AS, YY, and YK wrote the manuscript. All authors read and approved the final manuscript.

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ORIGINAL RESEARCH
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Procedural Memory Consolidation in Attention-Deficit/Hyperactivity Disorder Is Promoted by Scheduling of Practice to Evening Hours

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In young adults without attention-deficit/hyperactivity disorder (ADHD) training on a novel movement sequence results not only in large within-session (online) gains in task performance but also in additional (delayed, off-line) gains in the performance, expressed after an interval of sleep. In contrast, young people with ADHD, given an identical practice, were shown to improve online but expressed much smaller delayed gains overnight. As delayed gains in performance are taken to reflect procedural ("how to") memory consolidation processes, this may explain skill learning deficits in persons with ADHD. However, motor training is usually provided in morning sessions, and, given that persons with ADHD are often evening types, chronobiological constraints may constitute a hidden factor. Here, we tested the hypothesis that evening training, compared to morning training, would result in larger overnight consolidation gains following practice on a novel motor task in young women with ADHD. Participants with ($N = 25$) and without ($N = 24$) ADHD were given training on a finger opposition sequence tapping task, either in the morning or at evening. Performance was assessed before and immediately after training, overnight, and at 2 weeks post-training. Individuals with ADHD reported a general preference for evening hours. Evening training was equally effective in participants with and without ADHD, both groups showing robust consolidation gains in task performance overnight. However, the ability to express delayed gains overnight was significantly reduced in participants with ADHD if trained in the morning. Typical peers were as effective in expressing overnight consolidation phase gains irrespective of the time-of-day wherein the training session was afforded. Nevertheless, even after morning training, participants with ADHD fully retained the gains acquired within the first 24 h over an interval of about 2 weeks. Our results suggest that procedural memory consolidation processes are extant and effective in ADHD, but require that specific biobehavioral conditions be met. The affordance of training in the evening hours can relax some of the constraints on these processes in ADHD. The current results are in line with the notion that the control of what is to be retained in procedural memory is atypical or more stringent in ADHD.

Keywords: procedural learning, motor sequence, consolidation, attention-deficit/hyperactivity disorder, chronotype, evening training, young adults, training schedule

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INTRODUCTION

Motor Learning in Healthy Adults

Procedural memory processes (1–4) subserve the mastering and retention of motor skills and have been characterized in typical adults by a distinct time course (5–8). Large improvements in speed of motor performance occur early on during training on a novel motor task, with no costs of accuracy (i.e., within-session gains, "fast" learning phase). Performance within-session reaches an asymptote as practice accumulates [e.g., Ref. (5)]. However, within several hours after the end of the training session, additional robust gains in performance can be expressed (as delayed, "off-line" gains), reflected in improved speed and accuracy of task performance, as well as in a reduction in performance variance (9–11). The off-line gains are considered to constitute a behavioral marker for the successful accomplishment of procedural memory consolidation processes, which are initiated by the training experience but requiring hours to evolve; processes whereby the neuronal substrates engaged during practice are changed according to the accrued experience (3, 12–15). The level of motor performance attained at the consolidation phase is typically retained over a period of weeks and even months in young adults (3, 6, 7, 16). In the FOS task, the task used in the current study, these gains were correlated with experience dependent motor cortex activity pattern changes (17).

Training-related factors such as the number of task repetitions and instruction are critical in determining the effectiveness and course of skill learning (10, 18–20). However, after the termination of the training experience, conflicting experience, or the availability of a post-training sleep interval can also critically affect the course of learning a new skill, specifically, by interacting with the consolidation processes (8, 14, 21). Sleep has been identified as a state wherein the consolidation of newly acquired information in memory is promoted, depending on the specific conditions of training, instruction, and proximity to sleep episode (22, 23). Sleep supports both quantitative and qualitative changes of memory representations (5, 8, 15, 24–27), and age- or health-related changes in sleep architecture were shown to disrupt normal consolidation processes (23). In typical young adults training in the FOS task, memory consolidation processes (as reflected in the expression of delayed, off-line, gains in performance, but also in a decreased susceptibility to interference by subsequent conflicting experiences) were shown to be accelerated and successfully completed not only by a night's sleep but also by relatively shorter daytime naps (8). Thus, in the FOS task [with training in the standard protocol (5, 7, 8)], the evidence clearly indicates that rather than time *per se*, time in sleep is the critical factor gating the successful completion of consolidation processes, in both young adults and the elderly (28) [but not in preadolescent children (29)].

Attention-Deficit/Hyperactivity Disorder (ADHD) Condition and Motor Learning Deficits in ADHD

Attention-deficit disorder (ADD)/ADHD is a neurological condition characterized by inattention and/or hyperactivity–impulsivity that interferes with everyday functioning. While attention problems are recognized as a core deficit (30), deficits in executive functioning (e.g., fluency, planning, inhibition, and set-shifting) (31) and motor functioning (32–34) are recognized as key characteristics.

Some theoretical accounts implicate deficits in procedural memory (skill acquisition) as a central deficit in ADHD (35). Findings from structural and functional neuroimaging studies of brains of individuals with ADHD have revealed differences compared to typical peers in multiple brain systems including circuits implicated in repeated task performance and skill learning (36–39). It is not clear, however, whether these differences relate to a less effective acquisition, or deficient consolidation or retention processes in ADHD. A simple view of ADHD as a procedural memory deficit may need to be qualified. The evidence from studies of implicit (SRT task) and explicit learning of movement sequences in adults and children with ADHD is equivocal; some studies report deficits vis-à-vis typical controls (32, 33, 40) while in other task conditions, participants with ADHD were as effective learners as their typical peers (40, 41). Deficits in the sustained engagement of attention resources and reduced inhibition of incorrect responses (42) were proposed as important factors leading to ineffective learning in ADHD.

A number of studies wherein the FOS task was used as the to-be-learned task suggest that young adults with ADHD may exhibit an atypical procedural memory consolidation process rather than a critical deficit (32, 43, 44). For example, in a study that compared the time course of learning following the FOS training in young females with and without ADHD, the ADHD group exhibited normal within-session gains in performance speed, but the delayed gains measured at the 24 h post-training retest, were reduced (32). Given the pivotal role of procedural memory for everyday functioning (e.g., the skill of driving) (3, 4), it would be reasonable to expect that short-term motor deficiencies occurring in the individuals with ADHD would have to be at least partially compensated on the long run. Indeed, the study by Adi-Japha and her colleagues (32) demonstrated that the relative initial deficits in the expression of overnight delayed gains turned out to be temporary; the performance gap vis-à-vis typical peers training in an identical protocol diminished within a few days. The real potential of the individuals with ADHD to acquire novel skills may, therefore, be uncovered by manipulating factors that gate brain plasticity; for example, more stringent demands may be set on factors such as attention and arousal levels or post-training sleep quality and timing in ADHD. Indeed, some of the relative learning deficits, in persons with ADHD, could be corrected when training was shortened (32, 33, 44, 45) perhaps decreasing the burden of long repetitive practice on mechanisms of sustained attention (46). The upregulation of arousal levels, which are typically low in ADHD (47), for example, by the means of whole body vibration (48) and white noise (49) stimulation, has been shown to enhance both attention and motor performance.

In typically developing adults, sleep after practicing a new motor skill supports memory consolidation processes, contributing to the generation of stable, enhanced and long lasting procedural memory representations (5, 7, 50–52). A comorbidity of ADHD and sleep disorders is recognized; over 65% of individuals with

ADHD may present with one or more sleep disorders (53–56). A recent review suggests that sleep problems and ADHD interact in a complex bidirectional manner with sleep disturbances exacerbating or exacerbated by ADHD symptoms (53).

Chronotype, Sleep, and Learning in ADHD

Chronotype is an individual characteristic reflecting the time of day at which a person is "at his best" (57); "eveningness" (delayed sleep period, alertness reaches the maximum values at 11 p.m.) and "morningness" (advanced sleep period, alertness reaches the maximum at 8 a.m.) are the two extremes with most individuals in the general healthy population preferring the period between these extremes (58, 59).

Adult ADHD is associated with the evening chronotype (60–62). More than 40% of adults with ADHD display an evening preference; in age-matched healthy peers in general population, only 10.8% exhibit evening preference (63). Morning preference is switched, respectively, 40.2% in the typical population and 18.5% in ADHD. Greater eveningness correlates with the core symptoms of inattention and increased impulsivity; as eveningness is associated with shorter night sleep period, sleep debt may play a causal role in these symptoms (63). Additional evidence for a link between ADHD symptoms and circadian disruption comes from findings that seasonal affective disorder, a depression disorder directly linked to circadian disruption shows high comorbidity with ADHD (55, 64, 65). It was also suggested that the hyperactivity of people with ADHD may lead to sleep deprivation (66). The core symptoms of ADHD, such as inattention, impulsivity, and impatience, are typical outcomes of sleep deprivation in typical adults (67).

Consistent failure to meet basic sleep needs is currently viewed as a significant contributor to the cognitive and behavioral deficits in individuals with ADHD (53). As many as 70% of children and up to 83% of adults with ADHD have been reported as having sleep problems (68, 69) with sleep onset insomnia (SOI), the most common problem (54). A study that compared ADHD with and without SOI reported that 78% of adults with ADHD reported SOI, but when tested objectively by actigraphy, no difference in basic sleep parameters (duration and efficiency of sleep, as well as sleep onset latency) were found between those reporting or not reporting SOI (55). However, compared to typical controls, the participants with ADHD showed extended sleep onset latencies and lower sleep efficiency. Adults with ADHD also report reduced sleep quality, difficulty in getting to sleep, and difficulty in waking up (70). Individuals with ADHD were found to sleep on average an hour less than controls on nights prior to work days (but not prior to free days) and showed larger variability in bedtimes and sleep latencies (64). More than 60% of adults with ADHD reported increased sleepiness during day time (54, 55, 70). Delayed timing of melatonin secretion is systematically found in children and adults with ADHD (54, 55, 71). Rybak et al. suggested that a substantial circadian phase delay considerably impacts the core pathology of the ADHD (72).

Brain plasticity, the basis for skill and knowledge, is a slow and highly controlled (selective) process, wherein synaptic and cellular modifications occur at brain circuits in which the memory was initially encoded during salient experiences. Multiple lines of evidence suggest that these processes proceed "off-line," during both wakefulness and sleep, and culminate in the consolidation of new information and it's integration into previously existed knowledge (3, 5, 8, 15). Whether these off-line processes will be allowed to proceed to a successful completion is under strict control ("gating") (73). Optimal arousal level during encoding is considered a prerequisite gating factor mediating the long-term memory formation (47). Memory systems (74) and cognitive processes such as attention and executive functions (75, 76), as well as reward processes (77–79), are sensitive to disruptions of sleep and circadian rhythms. Indeed, the circadian clock, the reward system, and memory processes directly or indirectly affect neurogenesis and neural growth and shaping processes (80). Light acts on all three systems through common basic signaling pathways (80) and all three are affected by the hypothalamic–pituitary–adrenal axis *via* cortisol (81). Moreover, the evidence that most of the genes that shape the biological clock are expressed in brain areas that are associated with learning, memory, and reward, such as the amygdala, the hippocampus, and the ventral tegmental areas, is in line with the notion that the endogenous ~24 h time-generator (suprachiasmatic nucleus) has a role in gating neuronal plasticity following daily experiences (81).

The Current Study

The majority of training protocols used in memory research afford training sessions during morning or early afternoon, a time of day that may be suboptimal for individuals with evening chronotype and/or with higher susceptibility to interference [like the persons with ADHD (55) or the elderly (28)]. Recently, it was proposed that post-training sleep and its timing relative to the training experience is a critical factor in the control (gating) of motor skill memory selectivity in young adolescents (82) and in the elderly (28). Similar constrains may be imposed on mnemonic processes in individuals with ADHD during the morning hours so as to limit the generation of long-term memory from experiences gained in less than optimal practice-learning conditions; i.e., when alertness and cognitive abilities are at the diurnal minimum (83). Thus, memory deficits may be, at least in part, a result of the timing of the training experience rather than a general deficit in motor skill consolidation. In the current study, we tested the hypothesis that practice in the evening hours compared to morning hours may provide better conditions for the engagement of, the presumably atypical, consolidation processes in young women with ADHD. Operationally, we expected that training in the evening hours will result in higher delayed, overnight, gains in performance than training in the morning in the ADHD groups. In contrast, we expected that in the control groups (typical adults), delayed gains in performance will evolve regardless of the timing of training session.

We chose to address in the current study only young women with ADHD because (i) the performance of skilled movements in ADHD were suggested to be gender dependent (84, 85), (ii) between individual variances in the symptomatology of ADHD is smaller in females compared to males (86) and thus a smaller number of participants can be used in an exploratory study, and (iii) to enable a direct comparison to the results of previous studies (32, 44) wherein consolidation processes were

systematically explored in young women with ADHD, using the FOS task (the task used in the current study).

MATERIALS AND METHODS

The study was approved by the Human Experimentation Ethics committee of the University of Haifa and the participants signed an informed consent form in accordance with the Declaration of Helsinki before beginning the experiments. Subjects were paid 150 shekels (approximately $37) for their participation.

Participants

Forty-nine right-handed (87) young (age between 20 and 35 years) females, University of Haifa students, enrolled in the study. Participants were recruited through advertisement boards at the University of Haifa and the University center for students with disabilities, for a "motor learning and memory study." 24 participants met the criteria for a DSM-IV diagnosis of ADHD, and 25 typically developing adults matched by age and education, served as a control group. Inclusion criteria for the ADHD groups were as follows: (1) a formal psycho-didactic diagnosis of an attention-deficit disorder (either ADD or ADHD) from an authorized clinician, psychiatrist, or neurologist, approved by the University center for students with disabilities within 5 years of the current study; (2) a positive screening on the adult ADHD self-report scale (ASRS) (88, 89); and (3) no stimulant treatment for ADHD (methylphenidate or other stimulant drugs) during the recent period (> month). The participants of the ADHD group had on average 11 out of 18 items (10.9 ± 2.7, mean $\pm$ SD) positive responses on the ASRS. The control participants met less than 3 out of 6 criteria of the ASRS screening questionnaire (first 6 items). All control participants affirmed that they were not suggested (by family members or teachers) to have or were never diagnosed as having ADHD/ADD during their childhood or adulthood.

All participants underwent a semi-structured interview to exclude persons with diagnosed sleep, neurological or psychiatric disorders, motor-skeletal diseases, and use of chronic medications or drugs. Four of the participants with ADHD, but none of the participants in the control group, reported that they were previously diagnosed as having dyslexia. All participants underwent chronotype assessment using the Horne–Östberg Morningness–Eveningness Questionnaire (MEQ) (90). MEQ assesses whether a person's peak alertness is in the morning, in the evening, or in between. Higher sum scores are associated with morningness, while lower scores point to eveningness. The MEQ is a widely used and reliable scale to measure circadian type (91, 92).

Participants reporting skilled "blind" typing or professional string instrument playing and those reporting sleeping less than 6 h per night routinely, were excluded (5, 32, 43). The participants were instructed not to practice the study task that they were trained on between the scheduled meetings and not to drink caffeine containing drinks during the experiment.

Task and Procedure

The participants were trained and tested in performing an explicitly instructed five-element finger-to-thumb opposition sequence (**Figure 1A**) (5, 32). All tests were performed with the participants sited in the arm-chair with their left (task performing) arm positioned, comfortably extended, with the palm facing up to allow video recording of all finger movements. Visual feedback was not allowed; the participants were instructed to avert the gaze away from the fingers of the performing hand.

The experiment included three sessions. In the first session, lasting approximately 30 min, the experimenter showed the thumb-to-finger opposition movements, without demonstration of the sequence. Participants received verbal instructions, informed which sequence they were assigned to (randomly chosen A or B, **Figure 1A**) and performed self-paced warm-up

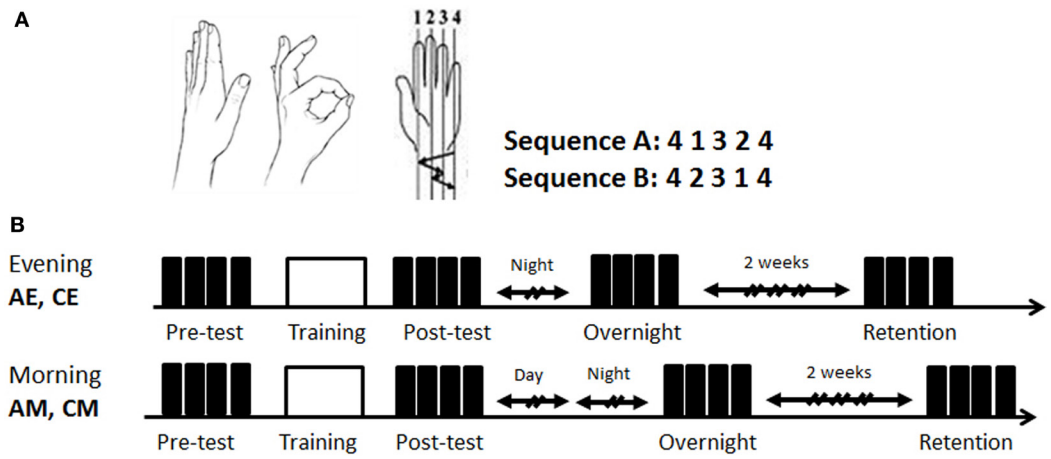

FIGURE 1 | Task and study design. **(A)** The finger-to-thumb opposition task. The two 5-element finger-to-thumb opposition sequences were mirror reversed order of movements to each other. Each participant was randomly assigned one of the sequences (A or B); **(B)** the time line of the two experimental conditions. All participants were trained in an identical single session (160 cued repetitions of the sequence) (white box) afforded either at 7:00 p.m. to 9 p.m. (evening) or at 8:00 a.m. to 10:30 a.m. (morning). Both the evening and the morning groups were retested in the morning hours of the next day. Performance was tested at four time-points: pretest, posttest, overnight, and 2 weeks retention post-training (black boxes—test blocks; h—hours). EA, ADHD training at evening; EC, typical controls trained at evening; MA, ADHD trained at morning; MC, typical controls trained at morning.

sequences three times. Following the correct performance of the three warm-up trials, a pre-training performance test, a training, and a post-training performance test were afforded. A performance test consisted of four self-paced blocks, each 30 s long. An explicit instruction was provided before each block to perform the assigned sequence of finger movements "as fast and as accurate as possible" between the start and the stop sounds, given by the computer. Occasional errors should not be corrected. A 30 s rest interval was afforded between the test blocks. Following completion of the four test blocks (pretest), the participants performed 20, 30-s, cued training blocks (training), with a 30-s rest between blocks, altogether 160 repetitions of the sequence. Rest periods could be prolonged if requested by the participant.

Start of each sequence was signaled by a beep at a rate 2.5 s per sequence. No feedback was provided on correctness and speed of performance. Following the training, participants again performed four test blocks (posttest), with identical instructions to the initial tests.

The participants were randomly assigned to four groups (**Figure 1B**): two groups, ADHD-morning (AM, $n = 12$) and control morning (CM, $n = 13$) were trained in the morning (8:00 a.m. to 10:30 a.m.); and two additional groups, ADHD-evening (AE, $n = 12$) and control evening (CE, $n = 12$), received an identical training session in the evening (7:00 a.m. to 9:00 p.m.) on the first day of the experiment. The first session (first day, evening, or morning) included the baseline performance test on the assigned sequence (pretest), the training session and the post-test. All participants were retested during second session in the morning of the next day (overnight retest, 5 min long). The third, retention test (third day session, 15 min long), took place on average 14 days (±2) after the second session and was performed again during morning hours (8:00 a.m. to 10:30 a.m.).

Participants were asked to wear an actiwatch (Actigraph Co.) starting from the end of the immediate post-training test to the next 5–7 days, so as to record sleep times and quality. Actigraphy was optional; a consent to wear an actiwatch did not constitute an inclusion criterion. The data were analyzed using ActiLife 6 software.

Statistical Analysis

Performance data were analyzed off-line in terms of speed (number of correct sequences) and accuracy (number of errors) performed per test block from video recordings. Average speed and accuracy of the four test-blocks at each of the four time points (pre-training; post-training; 12–24 h post-training; retention) was calculated. Speed and accuracy of performance were analyzed separately using: (a) a repeated measures analysis of variance with the four time points as within-subject factors × 4 groups [ADHD morning (AM); ADHD evening (AE); CM; CE] as a between subjects factor; and (b) a repeated measures analysis of variance with two consecutive time points to test performance changes across different stages of learning: acquisition phase—fast learning (pre-training vs. post-training), consolidation phase—slow learning (post-training vs. 24 h post-training) and retention phase (24 h post-training vs. retention). Two-tailed *t*-tests corrected for multiple comparisons were used in the analysis of the normalized performance gains with level of significance of $p < 0.05$.

RESULTS

Chronotype and Sleep Data

Mean group MEQ scores differed between persons with ADHD and healthy controls (two-sample *t*-test, $t = -4.127$, $p < 0.001$); lower scores, corresponding to larger eveningness were found for the ADHD group (**Table 1**). The proportion of participants expressing a certain chronotype was significantly different between the groups ($\chi = 9.17$, $p = 0.043$; Fisher's exact test, $p = 0.048$). More eveningness types were found in the ADHD group than in the control group (45.8 vs. 12%). Also, there was a significant difference between the ADHD and the control groups when the MEQ score (continuous measure) were compared (two-sample *t*-test, $t = 4.290$, $p < 0.001$). There was, however, no significant difference in the MEQ scores of the participants with ADHD who were trained in the morning as compared to those receiving evening training (two-sample *t*-test, $t = 0.660$, $p = 0.516$; EA group—5/12, MA group—6/13). Similarly, no significant difference in the MEQ scores of the control participants who were trained in the morning as compared to those trained in the evening was found (two-sample *t*-test, $t = -0.510$, $p = 0.615$; EC group—1/12, MC group—2/12).

As the participation in actigraphy was voluntary, the actigraphy data sample is limited and contains selected participants in each condition [ADHD $n = 16$, control $n = 12$; AM $n = 7$, AE $n = 9$, CM $n = 6$, CE $n = 6$]. Average time-in-bed, sleep latency (time to fall asleep), total sleep time (minutes), and sleep efficiency parameters, averaged across 5–7 nights starting from the first night following the training session, were analyzed using two-tailed independent sample *t*-tests. Results showed significant main effect of group (ADHD, control) for total sleep time ($t = -2.722$, $p = 0.011$), reflecting shorter night sleep in ADHD participants (ADHD: 400.18 ± 74 min, control: 498.46 ± 115 min). No significant differences were found with regard to sleep efficiency (mean 92.3 ± 8.6%), sleep latency (mean 4.3 ± 2.9 min) and time-in-bed. All participants reported a high subjective sleep quality during the experimental period. No significant correlations between chronotypes and sleep parameters and the observed gains in performance speed at the posttest, overnight, and retention test points were found.

Behavioral Data

First, we excluded the possibility of a confounding effect of pre-training differences in performance between the experimental

TABLE 1 | Morningness–eveningness questionnaire (MEQ) continuous and categorical scores for the ADHD and control participants.

Type	ADHD ($n = 24$)	Control ($n = 25$)
MEQ mean ± SE	42 ± 1.89	53.86 ± 2.03
Morning type	0	1
Moderately morning type	2	6
Neither type	11	15
Moderately evening type	7	3
Definitely evening type	4	0

The continuous scores were translated into categorical chronotypes using standard cutoff criteria (90, 91).

groups. Independent samples, two-tailed *t*-tests showed that there were no significant difference between the pretest performance of the two control groups (CM, CE) ($p = 0.12$) as well as between the two ADHD groups (AM, AE) ($p = 0.558$). There were also no significant differences between the participants with ADHD and their corresponding control groups when tested in the morning (MA, MC; $p = 0.22$) or in the evening (EA, EC; $p = 0.33$). Thus, the baseline performance of all participants was not significantly affected by the time of test (morning or evening) or ADHD status (**Figure 2**).

Training on the assigned sequence of movements resulted in early (within-session) and delayed (post-training, time-dependent) gains in performance triggered by a single training session in all groups (**Figure 2**). An analysis of variance with repeated measures (rm-ANOVA) with four groups × 4 time points, showed that, overall, there was a significant improvement in speed [$F(3, 43) = 78.46$, $p < 0.001$] (**Figure 2**, upper panel) across the study period in all groups. There was no significant group effect ($p = 0.705$). There was, however, a trend toward a significant interaction of time-point × group [$F(9, 135) = 1.78$, $p = 0.079$] suggesting that the performance changes were dissimilar across the four groups.

On average, the participants in all four groups tended to commit, if any, very few errors (**Figure 2**, lower panel). Absolute accuracy did not change significantly across the period tested [$F(3, 43) = 1.396$, $p = 0.247$], suggesting that in all groups the improvements in speed were not at the cost of increased errors.

To explore which of the time intervals contributed to the trend toward an interaction of time-point and group, in performance speed, *post hoc* rm-ANOVA comparing pairs of consecutive time-points were conducted across the four groups. A significant interaction of time-point × group was found only for the post-session consolidation interval, i.e., in comparing between the posttest and the overnight post-training retest [$F(3, 45) = 3.31$, $p = 0.028$]; indicating a significant difference in the rate of performance improvement overnight in the different groups. As can be seen in **Figure 2** (inset), the ADHD morning group lagged behind their peers who received the identical training protocol but in the evening, as well as behind the participants in the two control groups. To directly test the contribution of the time of training to the expression of overnight, delayed, gains in performance, in participants with ADHD, an rm-ANOVA was performed comparing the two time-points (posttest, overnight) in the two ADHD groups (AM, AE). Although there was no

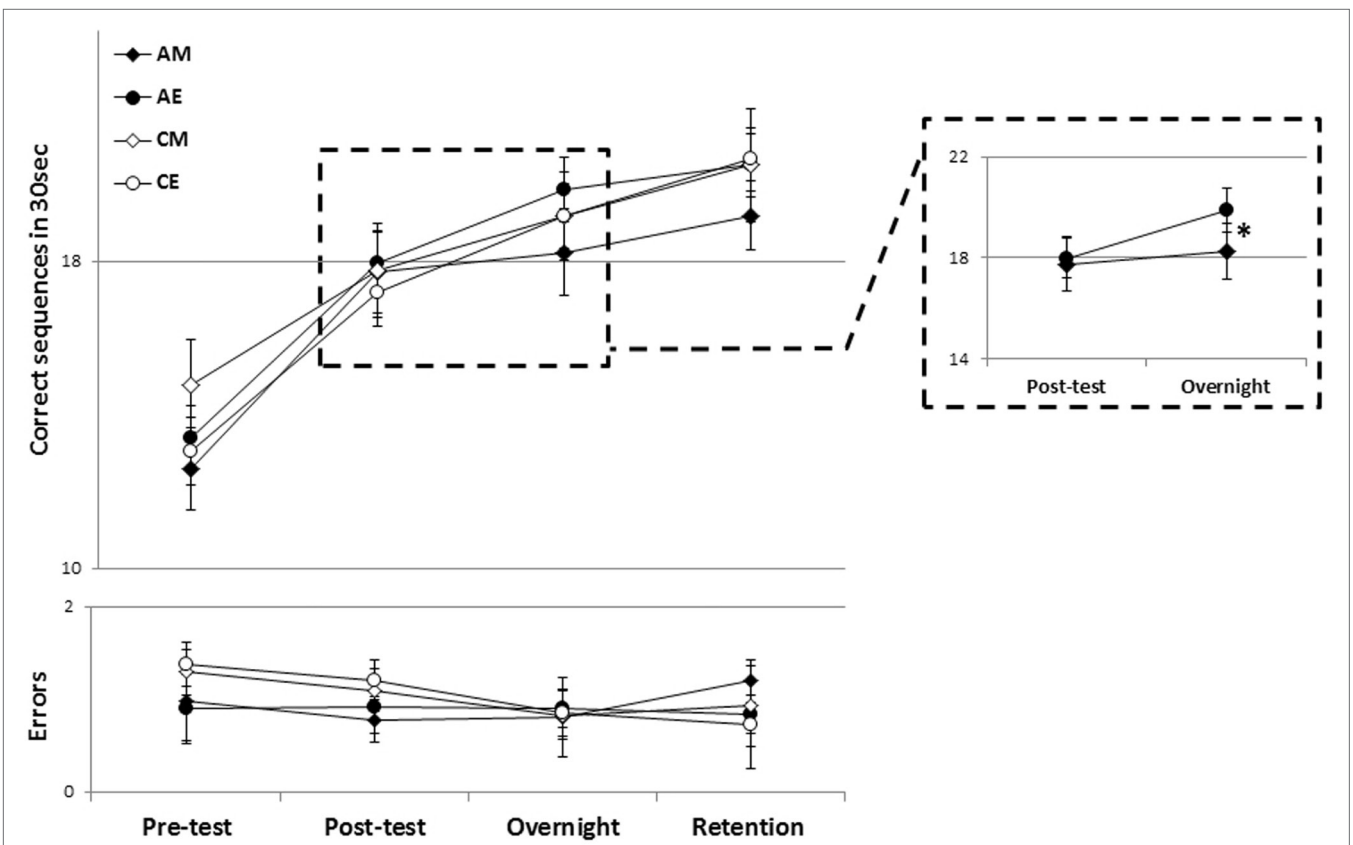

FIGURE 2 | The time course of performance improvement in the four groups. There were clear within-session gains as well as delayed (post-training) "off-line" gains in speed that were well maintained across a 2-week retention interval (upper panel) with no costs in accuracy (lower panel). Each data point depicts the mean group performance for four time-points. Note that the overnight time-point denotes performance on the morning of the post-training day (~12 or 24 h post-training for the evening and morning training groups, respectively). AM, ADHD morning; AE, ADHD evening; CM, control morning; CE, control evening (bars, SEM). Inset: a magnified view of the AM and AE groups' performance across the first overnight interval (consolidation phase). *Significant interaction effect.

significant group effect ($p = 0.49$), there was a significant time-point effect [$F(1, 22) = 22.24$, $p < 0.001$] indicating overall gains, but also a significant interaction of time-point × group [$F(1, 22) = 7.55$, $p = 0.012$] reflecting the smaller gains in the ADHD morning group (**Figure 2**, inset). A similar analysis comparing the overnight, delayed gains in performance speed in the two Control groups showed a significant overall improvement in both groups (CM, CE) [$F(1, 23) = 39.9$, $p < 0.001$] but no significant group (i.e., time of day) effect ($p = 0.58$) as well as, importantly, no significant time-point × group interaction ($p = 0.29$) suggesting that both groups improved at a similar rate.

The time of day in which training was afforded had, however, no significant effect on the ability to retain the gains in speed across the 2 weeks interval (**Figure 2**). An rm-ANOVA comparing performance in the last two time-points (overnight, retention) in the four groups showed that, rather than forgetting, there was a significant improvement in speed across the retention interval [$F(1, 45) = 12.26$, $p = 0.001$], but no significant group effect ($p = 0.788$), reflecting the finding that the gap that opened between the AM groups performance and that of their peers (irrespective of ADHD status) did not close at 2 weeks post training. The relatively smaller speed gains of the AM group were as well retained as those of the other participant groups.

Although there were no significant differences between the four groups' average performance, there were large individual differences in pre-training performance, irrespective of ADHD status. To ensure that these large differences between individuals' task performance levels did not bias the analyses based on absolute performance measures, we also assessed the differences in the expression of delayed gains in performance, with respect to the time of day training was afforded, using normalized data (**Figure 3**).

To this end, each participant's gains in the overnight post-training interval (i.e., the difference between overnight and post-test) were normalized to pre-training performance. In addition, normalization to pre-training performance was done for the total post-training gains expressed in the retention test (i.e., for the difference between retention and the immediate posttest) (**Figure 3**). There was a significant difference between the two ADHD groups (AM, AE) in the overnight interval (two-sample t-test, $t = -0.81$, $p = 0.042$) reflecting an advantage for the evening group. In addition, the overnight performance gains of the ADHD morning group were significantly smaller compared to the control participants trained in the evening (two-sample t-test, $t = -2.085$, $p = 0.05$) though not significantly smaller than the gains of the CM group ($p = 0.36$). However, the overnight gains of the ADHD evening group (AE) were not significantly different from the gains attained by their typical peers trained either at morning (CM) or evening (CE) ($p = 0.43$, $p = 0.54$, respectively). There were no significant differences in the normalized performance gains expressed over the 2 weeks retention period in the four groups.

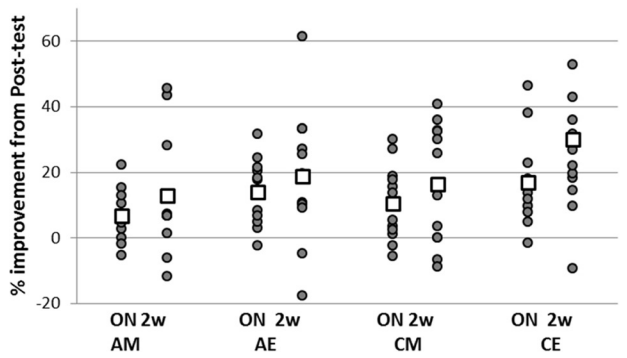

FIGURE 3 | Individual normalized gains in task performance speed expressed at overnight and retention. Overnight gains (ON—the difference between overnight and posttest) were normalized to performance in the posttest; total gains (2 w—difference between retention and the immediate posttest) were normalized to pretest performance for each individual participant. Positive values indicate delayed gains in task performance; negative values correspond to a slowing down of performance speed relative to immediate post training levels. Squares—group averages.

DISCUSSION

The present findings suggest that procedural memory consolidation processes are extant and effective in ADHD, but necessitate specific circadian conditions in order to be fully expressed. The current results, therefore, suggest a new effective learning strategy for ADHD. In line with previous studies (32), persons with ADHD showed the expected gains within the training session but less-than-expected performance gains, evolving overnight, during the procedural memory consolidation phase, if the training session took place in the morning hours. The same training experience afforded in the evening was equally effective in participants with and without ADHD, with both groups improving within-session as well as expressing additional, robust gains in task performance overnight. Nevertheless, morning training afforded to individuals with ADHD was as effective as evening training in terms of the ability to retain the gains acquired within the first 24 h post-training over an interval of about 2 weeks. Moreover, the retention of the training induced gains in performance was as effective in individuals with ADHD as in their typical peers with no ADHD.

Importantly, the current results show that the disadvantage of morning training for ADHD was not related to their ability to improve within session, regardless of the time of training. This result is in line with previous studies (32). However, the relative disadvantage of the morning trained individuals with ADHD was in their ability to express delayed, consolidation phase gains following their quite effective within-session learning. This relative performance lag was maintained over the retention interval.

Chronotype and Sleep

There is good evidence supporting the notion that the affordance of an interval of sleep after a training experience constitutes an important factor in the expression of practice-dependent delayed ("off-line") gains in the performance of the FOS task in young adults (5, 14, 93) and perhaps more so in elderly individuals (28). There are ample data suggesting that sleep structure may be atypical in persons with ADHD (54, 69, 94). In line with these notions, in the current study, individuals with ADHD tended to be evening chronotypes and to have on average shorter sleep

durations. However, the robust overnight expression of delayed gains in the performance of the FOS, in persons with and without ADHD, after evening training, suggests that the post-training sleep intervals were equally sufficient in both groups in supporting the consolidation process.

The prevalence of late chronotypes among young adults in general population is less frequent than in those with ADHD but still significant, reaching 10–15% (95, 96); the low number of participants with evening chronotype in the control groups of the current study is in line with these reported frequencies. However, little is known about the contribution of chronotype to memory in healthy typical individuals. Future studies should address whether evening persons in the general population, those with no ADHD symptoms, may benefit from scheduling of learning session to evening hours, in analogy to the effects found for persons with ADHD. This is especially pertinent in adolescence, a phase of development wherein the circadian profiles are skewed toward eveningness (97).

Procedural Memory Processes in ADHD

The current results provide support for several notions pertaining to skill memory processes in adults with ADHD. First, there is evidence suggesting that the acquisition and consolidation of a recently acquired memory trace, pertaining to a trained movement sequence, interact, but nevertheless constitute independent processes; each of these processes may require a different set of specific conditions to be effectively completed (15, 98, 99). Our results support this notion—young women with ADHD were as effective learners in the morning and evening hours as their typical peers, but they did differ in terms of their ability to subsequently (overnight) express consolidation phase gains. Thus, learning (acquisition, potentially reversible) and memory (dependent on consolidation) may differ from each other with regard to critically important control processes and gating factors. Proximity of evening training to sleep interval may be critical for successful engagement of consolidation processes for persons with ADHD. Not mutually exclusive is the possibility that, in the evening type persons, circadian factors affecting consolidation processes, for example, more effective synaptic tagging (100), are (also) at work.

A second notion is that while procedural memory mechanisms in young adults with ADHD may differ from those subserving skill consolidation in typical individuals, individuals with ADHD nevertheless can generate and effectively retain procedural memory. Atypical procedural memory consolidation processes in young adults with ADHD were indicated in previous studies of motor learning using the FOS task (32, 101). Nevertheless, in both studies, as well as in a study addressing FOS task learning and motor memory consolidation in adolescents with ADHD receiving methylphenidate treatment (43), there was clear evidence, despite atypical learning patterns, for effective long-term retention of skill in the individuals with ADHD. The current results, however, support the notion that young women with ADHD practicing the FOS task may differ from their typical peers in the conditions under which the engagement of consolidation processes occurs. Thus, young women with ADHD may atypically engage consolidation processes when trained in the morning, but not when trained in the evening.

A third notion concerns the training conditions. Conditions that are well suited for typical young adults may be less than optimal for individuals with ADHD. Thus, the apparent consolidation phase deficits in individuals with ADHD may reflect an interaction of the specific learning (and test) conditions with the individuals' predispositions and chronotype, rather than the latter's specific deficits *per se*. For example, Fox and colleagues (101) showed that halving (shortening) the training session may be beneficial for the training of persons with ADHD; perhaps because individuals with ADHD tend to commit more errors in tasks and tests that require multiple repetitions (33, 42, 45, 102). We extend this notion to account for time of training as an important condition, given that in people with ADHD show predominant chronotypes that are skewed toward eveningness. Optimal arousal level during encoding is considered to be a prerequisite, gating factor, mediating the process of long-term memory formation (47). Thus, the endogenous biological clock should be considered as gating factor to neuronal plasticity induced by daily experiences (81).

Altogether, we propose that consolidation processes are under stricter control in individuals with ADHD compared to their typically developing peers. A similar notion of extant procedural memory consolidation mechanisms that may be under stricter constraints compared to that of typical young adults has been recently suggested in explaining the findings in elderly individuals (28). Korman and her colleagues have shown that motor skill acquisition is well preserved in healthy elderly individuals, however, unless a post-training nap was afforded, overnight (consolidation phase, "off-line") gains were under-expressed. The current findings indicate a similar pattern, with evening training critical for the expression of the full potential for overnight gains, in young women with ADHD. Thus, in analogy to the case of the healthy elderly, we propose that the apparent deficits observed after morning training in individuals with ADHD may reflect suboptimal engagement of procedural, "how to" memory consolidation processes rather than a core deficit in procedural memory consolidation abilities *per se* [as suggested for example by Nicolson and Fawcett (35)]. We do not suggest that the processes underlying the hypothesized under-engagement (or stricter control) of procedural memory processes in healthy elderly and in young adults with ADHD are identical. The proposal rather is that, in both populations, some added constraints are imposed on the selection of what is to be maintained in long-term memory after a given learning experience, compared to the constraints imposed on consolidation processes in typical young adults. Different constraints on consolidation processes (rather than differences in the capacity to learn or generate long-term procedural memory *per se*) have also been indicated by recent studies addressing developmental effects in FOS consolidation, i.e., before and after puberty in typically developing individuals (20, 29, 103).

Limitations

Several considerations may limit the interpretation of our findings, given the different first retest periods across study groups trained in the morning and evening hours. Unequal time periods from training to subsequent testing may have contributed to

processes of interference or enhancement (104), independently of circadian optimal time-windows for skill acquisition.

An increased susceptibility to interference (e.g., by everyday activities, following training session for which the new movement sequence is irrelevant) was suggested as a mechanism for applying a stricter consistency criterion on what is to be incorporated into long-term procedural memory (28, 105). One could suppose that, in adults with ADHD, there is an increased susceptibility to interference experiences during the waking hours after the training session, leading to smaller consolidation gains in performance. This possibility should be further investigated. However, a recent study suggested that overall susceptibility to interference by a subsequent conflicting experience is not enhanced, but rather is reduced in young women with ADHD (44), compared to typical peers.

The protocol using different delay periods across study groups trained in the morning and evening hours (all groups were retested the next morning) was implemented in to neutralize the possible differences in performance resulting from the time of post-training testing. Thus, the morning groups had more time (~24 h) to consolidate the newly acquired knowledge compared to the evening groups (~13 h). If time *per se* would be the critical factor to determine the amount of the delayed gains in performance, one would expect to find different levels of overnight performance in the control (evening and morning) groups. However, our findings clearly indicate that this is not the case. As well, in order to control for the confounding effect of the different time-periods following training, we have tested for skill retention at 2-week post-training, allowing ample time to complete the memory consolidation process. The results clearly indicate that: (1) all groups show robust retention (thus no forgetting) and, in fact, additional gains compared to the performance at the first retest; (2) the morning trained ADHD group still lags behind. Thus, our data show no forgetting in time intervals as long as 12–14 days post-training, and support the main interpretation of our results, of the disadvantage of morning training in young adults with ADHD.

Further, we note that current results are limited to a population of highly functional young females with and without ADHD (university students). Additional studies should be conducted in males or mixed experimental groups and in different age groups to afford more general conclusions.

CONCLUSION

The current study provides evidence to suggest that in individuals with ADHD (frequently exhibiting evening chronotypes), training session afforded during morning hours negatively affect procedural memory consolidation (off-line, delayed) processes. Thus, individuals with ADHD may benefit from training protocols that have been optimized for their own advantage rather than from protocols optimized for their typical peers. Just as the length of the training session (101) or the spacing (rest periods) within and between practice sessions (106, 107) need to be taken into consideration when adapting training protocols for the benefit of persons with ADHD, an adjustment of the diurnal scheduling of the training protocol may be necessary for the full expression of the potential for skill acquisition and its consolidation in persons with ADHD.

ETHICS STATEMENT

The study was approved by the Human Experimentation Ethics committee of the University of Haifa and the participants signed an informed consent form in accordance with the Declaration of Helsinki before beginning the experiments. Subjects were paid 150 shekels (approximately $37) for their participation.

AUTHOR CONTRIBUTIONS

MK, IL, and AK conceived and designed the experiments. IL collected the data. MK and IL analyzed the raw data. MK made the statistical analysis and interpretation of the data. MK, IL, and AK wrote the article.

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Neurocognitive Impairments Are More Severe in the Binge-Eating/Purging Anorexia Nervosa Subtype Than in the Restricting Subtype

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Objective: To evaluate cognitive function impairment in patients with anorexia nervosa (AN) of either the restricting (ANR) or binge-eating/purging (ANBP) subtype.

Method: We administered the Japanese version of the MATRICS Consensus Cognitive Battery to 22 patients with ANR, 18 patients with ANBP, and 69 healthy control subjects. Our participants were selected from among the patients at the Kobe University Hospital and community residents.

Results: Compared to the healthy controls, the ANR group had significantly lower visual learning and social cognition scores, and the ANBP group had significantly lower processing speed, attention/vigilance, visual learning, reasoning/problem-solving, and social cognition scores. Compared to the ANR group, the ANBP group had significantly lower attention/vigilance scores.

Discussion: The AN subtypes differed in cognitive function impairments. Participants with ANBP, which is associated with higher mortality rates than ANR, exhibited greater impairment severities, especially in the attention/vigilance domain, confirming the presence of impairments in continuous concentration. This may relate to the impulsivity, an ANBP characteristic reported in the personality research. Future studies can further clarify the cognitive impairments of each subtype by addressing the subtype cognitive functions and personality characteristics.

Keywords: anorexia nervosa restricting subtype, anorexia nervosa binge-eating/purging subtype, MCCB Japanese version, neurocognitive impairment, subtype personality characteristics

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INTRODUCTION

Anorexia nervosa (AN) is a disease characterized by extreme anxiety about eating, a pursuit of weight loss, and a distorted body image [1]. Its mortality rate is exceedingly high, even when compared to psychiatric diseases that are generally chronic [2]. Although AN is known to be associated with both biological and psychosocial factors, its etiology is poorly understood, and no

effective treatment is yet available. Recent studies have implicated cognitive dysfunctions in the development and maintenance of AN [3], and researchers are increasingly interested in cognitive functioning in AN, including aspects such as set-shifting [4–7], central coherence [8, 9], visuospatial abilities [10], and decision-making [11, 12]. Of these aspects, consistent findings have emerged for set-shifting and central coherence [4–9]. Set-shifting is related to flexibility in task performance; therefore, set-shifting impairments hinder adaptation to unfamiliar situations. Weak central coherence, which is believed to induce an excessive focus on details at the expense of big-picture thinking, is reportedly a characteristic cognitive dysfunction in autism spectrum disorder [13]. The weak central coherence in AN is more pronounced in visuospatial tasks than in verbal tasks [4], and these cognitive dysfunctions are reportedly closely tied to core AN symptoms such as the morbid pursuit of thinness and body image distortions [8]. In relation to body image impairment, it has been suggested that compulsively repeated body checking may reinforce negative perception, resulting in distorted beliefs of body image [14]. One of the factors that can lead to increased number of body checking behaviors is body dissatisfaction, which is conceptualized as a multi-dimensional construct consisting of behaviors, cognition and affect; it has been reported to be a candidate of a risk factor for AN onset [15].

Cognitive dysfunctions in AN also affect social adaptation and interpersonal relationships, and this has further consequences for functional outcomes [16]. Cognitive dysfunctions in AN are therefore believed to be associated with AN's core symptoms and patients' social functioning.

AN manifests in a restricting (ANR) subtype, in which patients limit food consumption, and a binge-eating/purging (ANBP) subtype, in which patients exhibit cycles of large meals followed by purging behaviors. Both subtypes share core clinical symptoms including efforts to maintain abnormally low weight, a fear of obesity, and body image disturbances, but there are clear personality and behavioral differences between persons with ANR and those with ANBP [17–20].

As for cognitive functions, past subtype-comparison studies have reported conflicting results. Although the studies agree that weak central coherence and poor set-shifting are commonly found in AN generally, no agreement has been reached in terms of the severity differences of these cognitive domains between the subtypes [21–23]. Furthermore, there is no consensus about dysfunctions in other cognitive domains in AN subtypes [24]. One of the reasons could be that there has been no study to our knowledge that comprehensively evaluated the separable cognitive functions with uniform and standardized test batteries. It would be extremely important to use the consensus assessment batteries because the preceding studies on AN subtype differences in cognitive functions used different tests to evaluate the same cognitive domain, resulting in inconsistent interpretation of the findings. For example, Rose et al. used the Ravello Profile, a cognitive function assessment battery for eating disorders, which can evaluate domains such as performance IQ, Verbal IQ, Visuospatial Memory, Visuospatial Processing, Verbal Fluency, Executive Functioning [25]. However, it cannot evaluate cognitive domains yet to be shown as impaired since it includes only those scales related to cognitive dysfunctions that are considered specific to eating disorders.

Therefore, for this study, we chose to use the MATRICS Consensus Cognition Battery (MCCB), which was originally designed to evaluate cognitive functions in patients with schizophrenia [26–28] and is appropriate for comprehensively assessing basic cognitive functions in order to characterize the extensive cognitive domains of AN subtypes. Because patients frequently alternate between the ANR and ANBP subtypes [29], elucidating the neuropsychological differences and similarities between the subtypes may clarify the pathophysiology of AN.

We developed a Japanese version of the MCCB (MCCB-J) and confirmed its validity and reliability for Japanese patients with schizophrenia [30] and its utility for detecting cognitive dysfunctions in Japanese patients with bipolar disorder [31]. The MCCB has been used to study mental illnesses other than schizophrenia, such as posttraumatic stress disorder [32] and treatment-resistant depression [33], and it has been used to identify cognitive dysfunctions in many other disorders [34, 35]. Although a previous MCCB-based study of AN found no cognitive impairments [36], we aimed to comprehensively examine the neurocognitive features and cognitive functions in each AN subtype using the MCCB-J.

MATERIALS AND METHODS

Participants and Procedures

We consecutively recruited female outpatients or inpatients with AN at the Kobe University Hospital with a targeted age range of 15–60 years. An experienced psychiatrist confirmed AN diagnoses through the clinical interview and we included patients in partial remission who fulfilled all of the diagnostic criteria except for a sustained period of low body weight. The exclusion criteria included a history of drug or alcohol abuse, a comorbid psychopathology related to drug or alcohol abuse, imminent suicidality, any indication of severe mental illness necessitating inpatient treatment, any serious medical condition, a serious daily living impairment due to psychiatric symptoms, or an IQ below 80 as assessed on the Japanese Adult Reading Test (JART) [37]. JART is the Japanese version of the National Adult Reading Test (NART) that was developed to estimate IQ in native English-speaking patients, and its validity and reliability have been confirmed [38]. The presence or absence of illnesses in the exclusion criteria was checked by asking about current psychopathology and developmental history in the clinical interview and by reviewing the past medical records. No recruited subjects were excluded from the analyses based on these criteria or refused to participate. Forty participants met the diagnostic criteria for AN in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition [1], and did not meet any exclusion criteria. Twenty-two patients (8 inpatients and 14 outpatients) exhibited the ANR subtype (mean age 27.59 $\pm$ 11.96, mean BMI14.27 $\pm$ 2.68, mean level of education 13.36 $\pm$ 2.20) and 18 patients (8 inpatients and 10 outpatients) exhibited the ANBP subtype (mean age 30.61 $\pm$ 11.97, mean BMI16.79 $\pm$ 2.69, mean level of education 12.83 $\pm$ 1.95). The main diagnosis was either ANR or ANBP and there was no comorbidity including

another subtype of AN. Medications were taken by nine of ANBP (antidepressant, $n = 3$, antipsychotic, $n = 5$, benzodiazepine, $n = 1$) and six of ANR (antidepressant, $n = 2$, antipsychotic, $n = 2$, benzodiazepine, $n = 2$) at the time of assessment. The data were collected for two years between June, 2015 and June, 2017.

For healthy controls, we recruited 69 female community residents with ages between 15 and 60 years inclusive and no histories of any eating disorders or any other psychiatric disorders through personal contact and public advertisement in the local community. Demographic data for patients and healthy controls are summarized in **Table 1**.

Written consent was obtained from all participants. We also obtained the written informed parental consent for participants under the age 16. The study was conducted according to the standards of the Declaration of Helsinki and was approved by the Kobe University Hospital Ethics Committee.

Measures

AN severity was assessed using the Eating Disorder Examination-Questionnaire (EDE-Q) [39, 40]. As alluded to, each participant's IQ was measured with the JART, which is the validated Japanese version of the NART [37]. As mentioned, our neurocognitive assessments were based on the MCCB-J [30], which was administered by clinical psychologists who had completed MCCB-J training. The MCCB-J consists of 10 subtests that assess seven cognitive domains [41], including (1) processing speed, which is assessed using the Trail Making Test, part A (TMT-A), the Brief Assessment of Cognition in Schizophrenia–Symbol Coding test (BACS-SC), and the Category Fluency–Animal Naming test; (2) attention/vigilance, which is assessed with the Continuous Performance Test–Identical Pairs (CPT-IP); (3) working memory, which is assessed using the University of Maryland–Letter-Number Span test (LNS), and the Wechsler Memory Scale III Spatial Span test (WMS-SS); (4) verbal learning, which is assessed using the Hopkins Verbal Learning Test–Revised (HVLT–R); (5) visual learning, which is assessed using the Brief Visuospatial Memory Test–Revised (BVMT–R); (6) reasoning/problem-solving, which is assessed using the Neuropsychological Assessment Battery–Mazes (NAB); and (7) social cognition, which is assessed using the Mayer-Salovey-Caruso Emotional Intelligence Test's Managing Emotions component (MSCEIT-ME). Each participant completed the full MCCB-J during one session that took ∼90 min.

Statistical Analysis

Because our participants were all Japanese, we did not use the published MCCB normative data as reference data [42]. Instead, we computed T-scores from the means and standard deviations (SDs) of the Japanese normative data derived from the age-corrected standard scores from the MCCB scoring program [42]. The normative data for the MCCB-J are based on 202 participants from six Japanese cities. For all further analyses, we used data from our healthy controls as reference data.

We used one-way analysis of variance (ANOVA) to compare the ANR, ANBP, and healthy control groups for demographic and clinical characteristics. We then conducted *post-hoc* pairwise multiple comparisons corrections for significant differences with Tukey's test. We used analyses of covariance (ANCOVA) to compare the ANR and ANBP groups for chart-recorded minimum body mass indices (BMIs), BMIs at assessment, illness durations and EDE-Q controlling for three demographic variables (i.e., IQ, age, and years of education) as covariance.

For between-group comparisons of MCCB-J scores, we conducted a multivariate analysis of covariance (MANCOVA) with the seven MCCB-J domain T-scores as the dependent variables, the three groups as the subject variables, and the three demographic variables exhibiting significant between-group differences (i.e., IQ, age, and years of education) as covariates. We then applied Bonferroni multiple comparisons corrections for significant differences.

For the ANR and ANBP groups, we calculated partial correlation coefficients with the three demographic variables (i.e., IQ, age, and years of education) as control variables to determine how the chart-recorded minimum BMIs, BMIs at assessment, and illness durations correlated with MCCB-J neurocognitive performance scores.

All statistical analyses were conducted with SPSS version 12.0 (IBM, Armonk, NY). Statistical significance was defined as $p < 0.05$.

RESULTS

Clinical and Demographic Features

Table 1 displays the means and SDs for the three groups' demographic and clinical characteristics. The ANOVA revealed significant between-group differences in age [$F_{(2, 106)} = 3.22$, $p = 0.044$], education level [$F_{(2, 106)} = 12.18$, $p < 0.001$], and IQ [$F_{(2, 104)} = 3.93$, $p = 0.023$]. *Post-hoc* application of Tukey's test showed that the ANR group was significantly younger than the healthy controls ($p = 0.044$), but the ANBP group did not significantly differ in age from the healthy controls ($p = 0.43$) or the ANR group ($p = 0.68$). *Post-hoc* analysis of educational levels revealed that compared to the healthy controls, the ANR ($p = 0.002$) and ANBP ($p < 0.001$) groups had significantly fewer years of education. However, it revealed no significant difference between the ANR and ANBP groups ($p = 0.73$). In terms of IQ, *post-hoc* testing revealed no significant differences between the ANR group and the healthy controls ($p = 0.11$), between the ANBP group and the healthy controls ($p = 0.055$), or between the ANR and ANBP groups ($p = 0.92$).

Compared to the ANBP group, the ANR group exhibited significantly lower minimum chart-recorded BMIs ($F = 4.35$, $p = 0.045$) and BMIs at assessment ($F = 7.97$, $p = 0.008$). However, the two groups did not significantly differ in illness durations ($F = 0.19$, $p = 0.662$) or EDE-Q scores ($F = 0.60$, $p = 0.446$).

MCCB-J Neurocognitive Function Scores

Figure 1 and Supplementary Table 1 show the mean T-score profiles for the MCCB-J domains in the ANR, ANBP, and healthy control groups. The MANCOVA of MCCB-J domain scores revealed a significant overall group effect for neurocognitive domain performance [$F_{(14, 190)} = 3.617$, $p < 0.001$, Wilk's lambda $= 0.623$]. When domain-specific

TABLE 1 | Demographic and clinical characteristics of the subjects.

	ANR group (n = 19–21)	ANBP group (n = 16–18)	Healthy controls (n = 69)	Group comparisons[a]		*Post-hoc* comparisons
		Mean ± SD		Statistics	p-value	
Age (years)	27.59 ± 11.96	30.61 ± 11.97	34.36 ± 11.03	$F = 3.22$	0.044	ANR<HC($p = 0.044$)
Estimated IQ[b]	101.67 ± 9.02	100.53 ± 9.95	106.10 ± 8.50	$F = 3.93$	0.023	n. s.
Education (years)	13.36 ± 2.20	12.83 ± 1.95	15.26 ± 2.27	$F = 12.18$	<0.001	ANR<HC($p = 0.002$)
						ANBP<HC($p < 0.001$)
Chart-recorded minimum BMI (kg/m^2)	11.54 ± 1.98	12.92 ± 1.99	–	$F = 4.35$	0.045	ANR<ANBP
BMI at assessment (kg/m^2)	14.27 ± 2.68	16.79 ± 2.69	–	$F = 7.97$	0.008	ANR<ANBP
Illness duration (years)	9.29 ± 7.21	10.35 ± 7.24	–	$F = 0.19$	0.662	n. s.
EDE-Q total	2.06 ± 1.36	2.43 ± 1.37	–	$F = 0.60$	0.446	n. s.

ANR, anorexia nervosa, restricting subtype; ANBP, anorexia nervosa, binge-eating/purging subtype; IQ, intelligence quotient; BMI, body mass index; EDE-Q, Eating Disorder Examination-Questionnaire; SD, standard deviation; ns, not significant.

[a]Group comparisons; One–way analysis of variance for age, estimated IQ, and education. Analyses of covariance for chart-recorded minimum BMI, BMI at assessment, illness duration and EDE-Q total score.

[b]Estimated IQ, One-way analysis of variance revealed significant between-group differences, but the post-hoc Tukey's test revealed no such differences.

results were considered, we found significant group effects for the processing speed, attention/vigilance, visual learning, reasoning/problem-solving, and social cognition domains. These results survived the Bonferroni correction. *Post-hoc* comparisons to the healthy controls revealed that the ANR group scored significantly lower in the visual learning ($p = 0.019$) and social cognition ($p = 0.002$) domains and that the ANBP group scored significantly lower in the processing speed ($p < 0.001$), attention/vigilance ($p = 0.001$), visual learning ($p = 0.001$), reasoning/problem-solving ($p = 0.005$), and social cognition ($p = 0.004$) domains. Compared to the ANR group, the ANBP group scored significantly lower in the attention/vigilance domain ($p = 0.009$).

Figure 2 and Supplementary Table 2 show the mean T-scores of the MCCB-J subtests for the three groups. The MANCOVA showed a significant overall group effect [$F_{(20.184)} = 3.043$, $p < 0.001$, Wilk's lambda = 0.565]. Compared to the healthy controls, the ANR and ANBP groups scored significantly lower on the TMT-A, BACS-SC, LNS, NAB, BVMT-R, MSCEIT-ME, and CPT-IP subtests, but the significant group effects for the LNS and NAB subtests disappeared after Bonferroni corrections. *Post-hoc* comparisons with the healthy controls showed that the ANR group scored significantly lower on the TMT-A ($p = 0.017$), BACS-SC ($p = 0.006$), BVMT-R ($p = 0.018$), and MSCEIT-ME ($p = 0.003$) subtests and that the ANBP group scored significantly lower on the TMT-A ($p < 0.001$), BACS-SC ($p < 0.001$), NAB ($p = 0.007$), BVMT-R ($p = 0.001$), MSCEIT-ME ($p = 0.004$), and CPT-IP ($p = 0.001$) subtests. Compared to the ANR group, the ANBP group scored significantly lower on the CPT-IP subtest ($p = 0.008$).

Correlations Between Clinical Characteristics and Neurocognitive Functioning Scores

As shown in Supplementary Table 3 and Supplementary Figure 1, MCCB-J neurocognitive performance scores did not correlate with chart-recorded minimum BMIs (ANR group: $-0.361 \leq r \leq 0.082$, ANBP group: $-0.407 \leq r \leq 0.269$), BMIs at assessment (ANR group: $-0.197 \leq r \leq 0.303$, ANBP group: $-0.343 \leq r \leq 0.358$), or illness durations (ANR group: $-0.270 \leq r \leq 0.290$, ANBP group: $-0.112 \leq r \leq 0.507$).

DISCUSSION

We aimed to comprehensively examine the cognitive characteristics of patients with the AN subtypes ANR and ANBP by using the MCCB-J, a comprehensive cognitive assessment for Japanese patients with schizophrenia, to systematically compare cognitive functions in patients with either subtype to those in healthy controls.

We found that compared to the healthy controls, both patient groups scored significantly lower in the visual learning and social cognition domains, with the ANBP group also scoring significantly lower in the processing speed, attention/vigilance, and reasoning/problem-solving domains. Furthermore, compared to the ANR group, the ANBP group scored significantly lower in the attention/vigilance domain. However, the patient groups and healthy controls achieved similar scores in the verbal learning and working memory domains. These results clearly characterized the cognitive dysfunctions of each AN subtype. Furthermore, we found no statistically significant correlations between the cognitive variables and BMIs or illness durations, which suggests that emaciation does not affect the cognitive variables.

The MCCB, which assesses seven cognitive domains with 10 subtests that have superb tolerability, practicality, and test-retest reliability, can be used repeatedly [41]. Another specific quality of the MCCB is its co-norming with a healthy population for standardization [42]. The seven cognitive domains were chosen because (1) they are potential targets for novel schizophrenia treatments, (2) they were examined in many past studies on cognitive dysfunctions in schizophrenia [43], and (3) they were

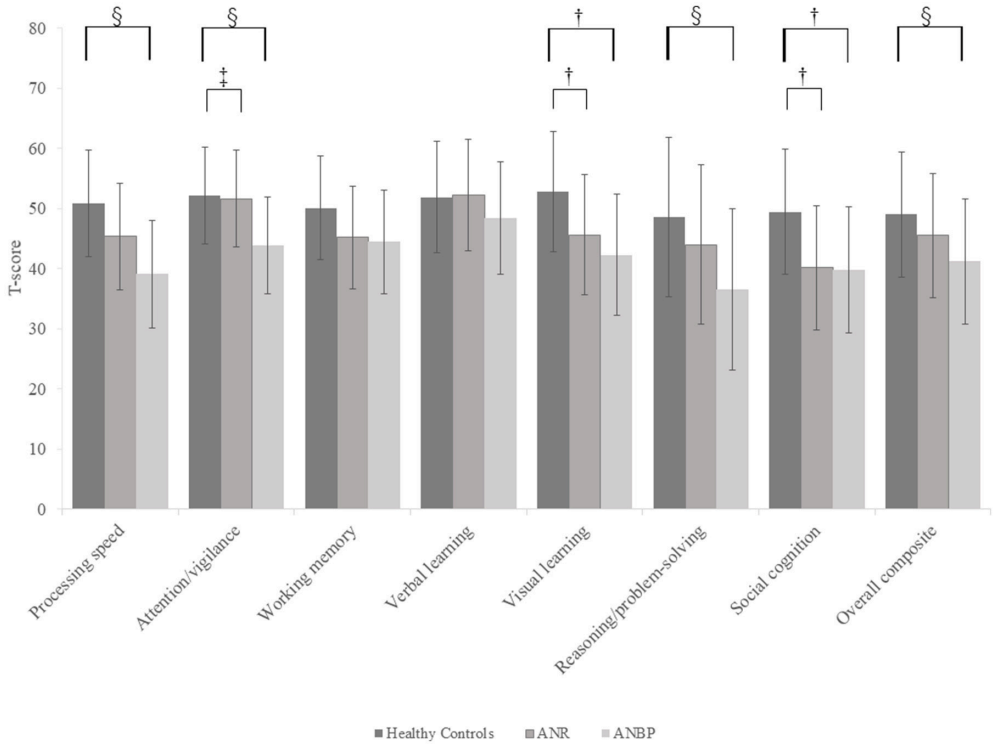

FIGURE 1 | Multivariate analysis of covariance for all MCCB-J domains and overall cognitive composite T-scores of the subjects. Mean T-scores for all MCCB-J domains and overall cognitive composite scores for the subjects. Error bars show standard deviation. ANBP, anorexia nervosa, binge-eating/purging subtype; ANR, anorexia nervosa, restricting subtype; MCCB-J, MATRICS Consensus Cognitive Battery, Japanese-language version. †Significant pairwise differences between the healthy controls and both the ANBP and ANR groups ($p < 0.05$). ‡Significant pairwise difference between the ANBP and ANR groups ($p = 0.009$). §Significant pairwise difference between the ANBP group and the healthy controls ($p < 0.005$).

separable neurocognitive factors previously examined in healthy controls using the Wechsler Adult Intelligence Scale III and Wechsler Memory Scale III [44]. Thus, the MCCB defines separable neurocognitive domains from healthy control data and incorporates the cognitive characteristics of schizophrenia.

The processing speed domain was assessed with the TMT-A and BACS-SC, which both measure processing speed through non-verbal domains, and a category fluency test, which assesses it through verbal domains. Both patient groups scored significantly lower on the TMT-A and BACS-SC than the healthy controls did, but there were no significant differences in category fluency scores. The TMT-A scores in particular were the lowest subtest scores for both AN groups. The TMT is among the most frequently used assessment tools for set-shifting [5–7, 17, 21, 23], which is characteristic of AN-associated cognitive dysfunctions. The TMT consists of part A, in which subjects serially connect numbers, and part B, in which subjects serially connect numbers and letters in turn. Although only the TMT-A is incorporated into the MCCB, the low TMT-A scores, which reflect TMT-B scores [45], suggest that cognitive flexibility is impaired in AN. Another characteristic of both AN groups in the processing speed domain was that non-verbal processing was slow whereas verbal processing was normal. This implies that although verbal information can be processed normally, visual information processing is problematic. As for overall processing speed domain scores, only the ANBP group scored significantly lower than the healthy controls because the ANBP group's TMT-A and BACS-SC scores were extremely low when compared to those of the healthy controls.

We evaluated the attention/vigilance domain with the CPT-IP, in which subjects press a button when identical numbers appear on a computer screen. This test measures sustained attention. The ANR group's CPT-IP scores were similar to those of the healthy controls, which suggests the absence of serious attention-arousal problems. However, the ANBP group scored significantly lower than both the healthy controls and the ANR group, which suggests that continuous concentration is impaired in ANBP. This represents the first report of CPT-IP-measured differences in continuous concentration between the ANR and ANBP subtypes. It should be emphasized that attention/vigilance was the only MCCB-J cognitive function domain for which we found a significant difference between the subtypes.

In the reasoning/problem-solving domain, we again found that the ANBP group scored significantly lower than the healthy controls did whereas the ANR group did not. We evaluated reasoning/problem-solving abilities with the NAB, which uses

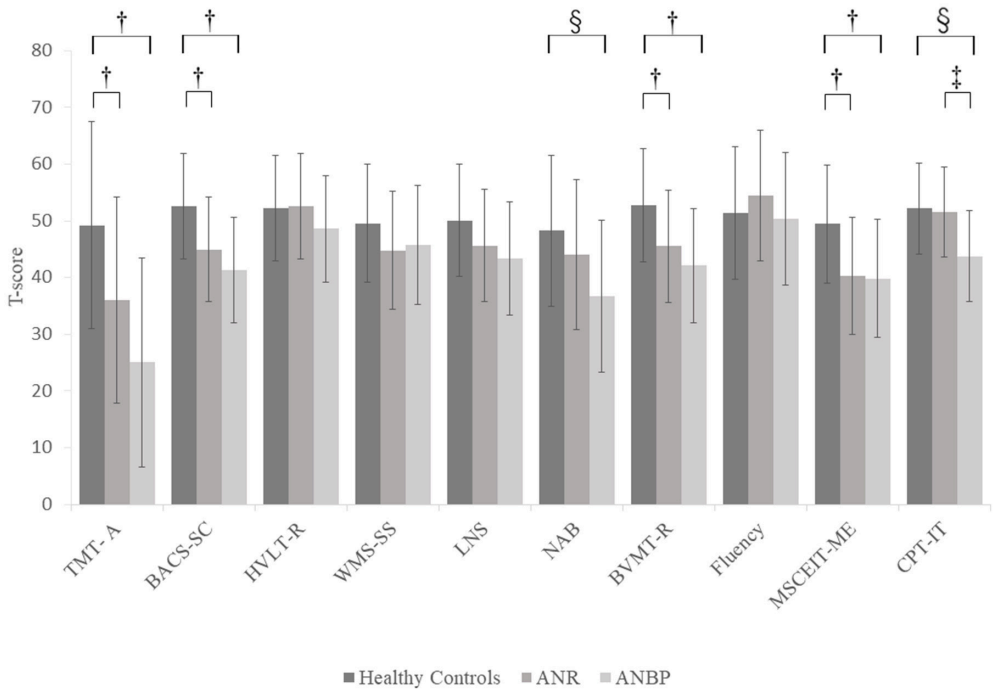

FIGURE 2 | Multivariate analysis of covariance for MCCB-J subtest T-scores of the subjects. Mean T-scores for all MCCB-J subtest scores for the subjects. Error bars show standard deviation. ANBP, anorexia nervosa, binge-eating/purging type subtype; ANR, anorexia nervosa, restricting subtype; BACS-SC, Brief Assessment of Cognition in Schizophrenia–Symbol Coding test; BVMT-R, Brief Visuospatial Memory Test-Revised; CPT-IP, Continuous Performance Test–Identical Pairs; Fluency, Category Fluency–Animal Naming test; HVLT-R, Hopkins Verbal Learning Test-Revised; LNS, University of Maryland–Letter-Number Span test; MCCB, MATRICS Consensus Cognitive Battery, Japanese-language version; MSCEIT-ME, Mayer-Salovey-Caruso Emotional Intelligence Test, Managing Emotions component; NAB, Neuropsychological Assessment Battery–Mazes; SD, standard deviation; TMT-A, Trail Making Test, part A; WMS-SS, Wechsler Memory Scale III Spatial Span test. †Significant pairwise differences between the healthy controls and both the ANBP and ANR groups ($p < 0.05$). ‡Significant pairwise difference between the ANBP and ANR groups ($p = 0.008$). §Significant pairwise difference between the ANBP group and the healthy controls ($p < 0.01$).

drawn mazes to assess insight and planning abilities that are related to conceptual understanding and objective observation capacities. Since attention and concentration are related to these conceptual activities [45], the ANBP group scored significantly lower in this domain than the healthy controls did, as was the case for the attention/vigilance domain. These results suggest that patients with ANBP experience difficulties in organization and planning.

For the working memory domain, we used the WMS-SS for non-verbal working memory and the LNS for verbal working memory. On the WMS-SS, neither patient group scored significantly lower than the healthy controls did. There were also no significant differences on the LNS after Bonferroni corrections or in pairwise comparisons of the healthy controls with either patient group. Therefore, in this study, working memory was intact in both AN subtypes.

We assessed the verbal learning domain with the HVLT-R and found that neither patient group significantly differed from the healthy controls. The ANR group in particular scored similarly to the healthy controls. Together with the fact that the ANR group scored higher than the healthy controls in the category fluency test, which reflects verbal processing speed, this implies that verbal domains are not impaired in the ANR subtype. Our results are consistent with those of a previous report [46] that language domain performance in patients with AN is no different from, and sometimes superior to, that of healthy controls.

We assessed visual learning with the BVMT-R, on which both patient groups scored significantly lower than the healthy controls did. These results confirm those of previous studies [10, 47] that reported impaired visual perception and visuospatial abilities in both AN subtypes. Visuospatial impairments and weak central coherence at the visuospatial level were the most frequently targeted impairments in the past AN-related studies, and those studies reported that these cognitive dysfunctions affect AN's onset and duration [4]. Of the available visuospatial domain measures, the Rey-Osterrieth Complex Figure Test (RCFT) [48], in which subjects copy a complex figure and later reproduce it from memory, has been the most commonly employed and is included in the Ravello Profile [25] that serves as a cognitive function battery for patients with AN. Although the BVMT-R that is included in the MCCB utilizes a simpler figure than the RCFT does, both patient groups scored significantly lower than the healthy controls did. This finding confirms the visuospatial memory and cognition impairments of both AN subtypes as reported in previous studies [10, 47] and further implies the seriousness of these impairments since lower

scores were obtained even with the BVMT-R's relatively simple test.

Cognitive function domains can be classified into neurocognitive domain and social cognitive domain. Social cognition consists of mental processes that underlie social interactions and is defined as the ability to perceive others' intentions and internal states [49]. The impairment of social cognition is reported to have a close relationship with daily living functions, and also associated with functional outcome [50]. In our current study, both ANR and ANBP were impaired in the social cognitive domain. Interestingly, although the ANR group's impairments in some neurocognitive domains were milder than those of the ANBP group, both groups exhibited similarly low social cognition domain scores. This finding may mean that ANR has comparable impairments in daily living functions as ANBP. AN-related social cognition impairments have been widely studied, and previous studies reported impairments of facial cognition [51] and theory of mind [52–54]. The MSCEIT-ME, which measures emotional control in conflictual situations, revealed that both AN groups had problems with such emotional control. Our results suggest that both AN subtypes have social cognition domain impairments, as previously reported, and that these impairments specifically affect emotional control in conflictual situations.

As noted, our ANBP group exhibited broader cognitive function impairments than our ANR group did. Our study is the first to report this subtype-specific difference in cognitive dysfunction severities. Clinical experiences also suggest that patients with ANBP more frequently exhibit kleptomania, substance dependence, suicide, and self-mutilation, which are all related to the impulsivity often observed in ANBP [17, 55], as well as comorbid depression and mood lability [56]. A longitudinal study also reported lower remission rates and higher mortality rates for patients with ANBP and poor prognoses [54]. The broader cognitive impairments of ANBP observed in our study are consistent with these clinical features, and, conversely, more severe cognitive impairments may be related to these features.

Our results reinforce previous reports that cognitive impairments in AN do not correlate with BMIs or illness durations [6, 7, 21, 47, 57, 58]. It is reported that cognitive impairment could be a marker of chronicity in AN or a risk indicator for the development of chronic AN [59]. Furthermore, set-shifting impairments, which have been observed in unaffected sisters of AN probands [21] and in patients with AN who recovered to normal weight [4, 60], could be an endophenotype [61]. This suggests that the cognitive impairments seen in AN may be traits unrelated to ill state.

Phillipou et al.'s study [36] is the only previous one to our knowledge that examined cognitive functions in AN with the MCCB, and it revealed that relative to healthy controls, the patients had significantly delayed false alarm responses on the CPT-IP and significantly different scores on the WMS-SS backward component but no significant differences in cognitive domain scores or subtest scores. But the authors noted that overall cognitive functioning was unimpaired in AN with the MCCB. These findings differ from ours, probably due to differences in the subjects. Phillipou et al. selected subjects who were medically stable but had suboptimal BMIs to minimize the influence of malnutrition on their results. Although our subjects were medically stable and had an average BMI comparable to that of Phillipou et al.'s subjects, our subjects had a greater average age and longer average illness duration. Also our subjects were distinctive in terms of its very low BMIs compared to previous studies [21, 60]; chart-recorded minimum BMIs of ANR being 11.54 ± 1.98 (kg/m^2) and that of ANBP 12.92 ± 1.99 (kg/m^2). ANBP showed higher mean EDE-Q scores than ANR, but this was not statistically significant. The reason could be that the EDE-Q scores may not necessary corresponds to the severity. As for relationship between illness severity and cognitive function, Phillipou et al.'s milder cases showed no significant cognitive impairment relative to healthy controls. The current study, which included more severe cases, showed cognitive domains with significantly lower cognitive functioning. These findings may suggest that cognitive function of our subjects was more impaired because the illness was more severe with very low chart-recorded minimum BMIs. Furthermore, cognitive impairments in the ANR group were milder than in the ANBP group in the current study, despite the ANR group having significantly lower minimum chart-recorded BMIs and BMIs at assessment. It is therefore unlikely that malnutrition directly relates to cognitive impairment, so just as a previous study [59] suggested that cognitive impairments are a risk factor for chronicity.

Any contribution of comorbid conditions such as depression and anxiety need to be discussed as well. Our current study could not examine the influence of comorbidity since there were no cases with comorbid depressive disorders or anxiety disorders. According to the data of the preceding studies [5, 9], neuropsychological performance did not correlate with level of anxiety and depression, which suggests that comorbid symptoms such as depression and anxiety may not influence cognitive functions.

This study has some limitations. It was a cross-sectional study, so it could not capture the whole picture of AN. Future prospective and longitudinal studies might provide more in-depth findings about subtype-specific cognitive impairments. Another limitation was that the sample size was relatively small. Future studies with larger samples are needed to validate our findings.

In summary, we found that MCCB-J scores for the visual learning and social cognition domains were significantly lower in both AN subtypes. Furthermore, the ANBP group scored lower than the ANR group did in all MCCB-J cognitive domains, which indicates broader cognitive impairments in ANBP. It was especially notable that we observed a difference in the attention/vigilance domain. This may relate to the impulsivity, an ANBP characteristic reported in the personality research [17–20]. Future studies may clarify the factors that contribute the development of eating disorders by examining the relationship between cognitive functions and psychological profile of ANR and ANBP including perfectionism characteristic to ANR. As this is the first systematic study of the previously unclear subtype-specific differences in cognitive impairments in AN, our results may be extremely valuable for future efforts to design treatment strategies and elucidate the pathophysiology of AN. We expect

that targeting the cognitive profile characteristics observed in our study will prevent severe and enduring AN and enhance improvements in social functioning.

AUTHOR CONTRIBUTIONS

HT and IS designed the study. HT, YK, and IS collected the data. AO administered the psychological tests. YA and SM analyzed the data. HT, RC and AO wrote the draft. HT and IS wrote the final manuscript. All authors approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2018.00138/full#supplementary-material

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