Treating Working Memory Deficits in Schizophrenia: A Review of the Neurobiology

Tristram A. Lett, Aristotle N. Voineskos, James L. Kennedy, Brian Levine, and Zafiris J. Daskalakis

Cognitive deficits are a core feature of schizophrenia. Among these deficits, working memory impairment is considered a central cognitive impairment in schizophrenia. The prefrontal cortex, a region critical for working memory performance, has been demonstrated as a critical liability region in schizophrenia. As yet, there are no standardized treatment options for working memory deficits in schizophrenia. In this review, we summarize the neuronal basis for working memory impairment in schizophrenia, including dysfunction in prefrontal signaling pathways (e.g., γ-aminobutyric acid transmission) and neural network synchrony (e.g., gamma/theta oscillations). We discuss therapeutic strategies for working memory dysfunction such as pharmacological agents, cognitive remediation therapy, and repetitive transcranial magnetic stimulation. Despite the drawbacks of current approaches, the advances in neurobiological and translational treatment strategies suggest that clinical application of these methods will occur in the near future.

Key Words: Cognition, EEG, neurophysiology, schizophrenia, TMS, working memory

Schizophrenia is a common and chronic psychiatric disorder characterized by delusions, hallucinations with concomitant cognitive, organizational, and motivational impairments. Currently approved pharmaceutical treatments for schizophrenia are typically effective for positive symptoms but have little or no effect on cognitive impairment (1). This is of particular concern, because cognitive performance is a key determinant of long-term outcome and mortality in schizophrenia (2). Cognitive dysfunction in schizophrenia shows high prevalence, is relatively stable over time, and is independent of psychotic symptoms (3). Moreover, cognitive dysfunction is present in healthy relatives of schizophrenia patients, and it has been suggested as a biomarker of schizophrenia (4). As a consequence, disturbances in critical cognitive process, such as working memory, are regarded as a core feature of schizophrenia.

Of the demonstrated neurocognitive deficits in schizophrenia, research has focused on working memory, which has been defined as the ability to transiently hold and manipulate information to guide goal-directed behavior (5). The contents of working memory are constitutively updated, monitored, and manipulated in response to immediate processing demands (5). Working memory prolongs the impact of experience beyond immediately accessible information to enable the incorporation of information from long-term memory, lexical labels, and other events into goal-oriented behavior (6). The dorsolateral prefrontal cortex (DLPFC) is crucial to working memory function in healthy adults (7). In schizophrenia patients, working memory deficits are associated with dysfunction of DLPFC as well as DLPFC connectivity with other regions and disruption of neurotransmitter input (e.g., γ-aminobutyric acid [GABA], glutamate, and dopamine) (8–10). Working memory in schizophrenia might also have a genetic basis. Schizophrenia patients and their unaffected co-twins perform significantly worse than control subjects on spatial working memory tasks (11). The letter-number-sequencing task (a measure of working memory) has been identified as an endophenotype of schizophrenia with a heritability of .39 (.25–.52) (12). Thus, improved identification of circuit disruption (from DLPFC to other regions) can help provide insights into the pathophysiology of working memory impairment in schizophrenia and the development of novel therapeutic interventions.

In this article, we review the neuropsychological and neuroanatomical basis of working memory and its relationship to schizophrenia. Next, the therapeutic approaches for treatment of working memory deficits in schizophrenia are discussed, including pharmacological interventions and cognitive remediation therapy (CRT). Finally, we establish the neurophysiological basis for working memory deficits and present repetitive transcranial magnetic stimulation (rTMS) as a potential novel therapeutic strategy.

Working Memory

A key benefit of studying working memory is that psychology and cognitive neuroscience have built a comprehensive framework for understanding the cognitive architecture of working memory and its neural correlates. For instance, studies in nonhuman primates suggest that lesions to the prefrontal cortex (PFC) cause marked reduction in working memory function and that subdivisions of the PFC might represent multiple working memory domains, each having its own specialized processing or content-specific storage (13,14). According to the seminal theoretical model by Baddeley (5), working memory functions can be fractionalized into specialized systems that serve as buffers for the storage and manipulation of information. The model is complemented by empirical evidence that most primate electrophysiology and neuroimaging studies, regardless of experimental procedure, report delay-period activity in the PFC [for examples, see (15,16)].

The PFC is an integral component of executive functioning (e.g., complex attention, planning, and mental flexibility) (17). The PFC contributes to working memory by exerting top-down control through filtering and strategic reorganization of

From the Centre for Addiction and Mental Health (TAL, ANV, JLK, ZJD); Institute of Medical Science (TAL, ANV, JLK, ZJD); Department of Psychiatry (ANV, JLK, ZJD); Department of Psychology (BL), University of Toronto; and the Rotman Research Institute (BL), Baycrest Centre Toronto, Toronto, Ontario, Canada.

Address correspondence to Zafiris J. Daskalakis, M.D., Ph.D., Temerty Chair in Therapeutic Brain Intervention, Professor of Psychiatry, University of Toronto, Centre for Addiction and Mental Health (CAMH), 1001 Queen Street West, Toronto, Ontario, M6J 1H4 Canada; E-mail: Jeff.Daskalakis@camh.ca.

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information (18). Therefore, working memory performance would depend on efficient communication to the PFC and its capacity to inhibit extraneous information. Top-down attention relies on parietal and prefrontal regions that largely overlap with activation during working memory tasks in both these regions (19). Moreover, high global brain connectivity to the DLPFC predicts better working memory performance as well as general fluid intelligence (20). The PFC thus acts as a flexible hub by which frontal connectivity is adjusted according to task demands (21).

More recently, research has emphasized recruitment of extrafrontal regions involved in perceptual or long-term representations in orchestration with DLPFC (22). Electroencephalagram (EEG) studies show theta coupling between prefrontal and parietal cortices is increased with more complex manipulation (23), memory load (24), and predict individual working memory capacity (25). Theta phase synchrony between the prefrontal and temporal cortices occurs during the maintenance phase of working memory (26) in addition to encoding and retrieval (27). Further evidence for medial temporal lobe involvement comes from intracranial EEG recording in human epilepsy patients that shows cross-frequency coupling of oscillatory activity in the hippocampus between beta/gamma range and the theta band, and the precision of coupling predicts working memory performance (28). This sustained phase synchronization between higher-order sensory, frontal, and temporal cortices and the hippocampus provides a mechanism for working memory maintenance by which activity in different brain regions is sustained in the absence of direct sensory output (26). An important consequence of these findings is that working memory depends on network-level activation and coordination.

Working Memory and Schizophrenia

Schizophrenia patients are cognitively compromised on the order of magnitude 1.0–1.8 SDs below the normal mean (29). Patients with an earlier onset have more severe cognitive deficits that persist throughout the course of the disorder (30). Cognitive impairments are present in the prodromal period and might contribute to heterogeneity in patterns of cognitive changes across illness phases and among individuals (31). Meta-analyses in schizophrenia demonstrate large deficits in all 3 domains of working memory (phonological, visuospatial, and central executive) with no clear differences across domains or tasks (32,33). There was also no consistent association between duration of illness, antipsychotic medication, or symptom profile and working memory in schizophrenia (33).

The DLPFC has been identified as a key liability region for working memory dysfunction in schizophrenia (34). In an early study, healthy individuals demonstrated increased blood flow to the DLPFC during the Wisconsin Card Sorting Task that was not observed in medication-free schizophrenia patients (35). However, recent neuroimaging studies generated conflicting findings with regard to DLPFC activation during working memory tasks. Both "task-related hypofrontality" and "task-related hyperfrontality" have been reported in patients with schizophrenia relative to healthy subjects (34). These discrepancies are potentially driven by study differences in task performance or difficulty, although it is possible that the findings are confounded by coupling and activation in other cortical regions. For example, stronger activation of deep brain structures [e.g., thalamus (36)] and the anterior cingulate cortex (37) in schizophrenia patients might be a product of compensatory mechanism for working memory deficits. Therefore, working memory dysfunction could be a result of reduced function of specific regions but also an impairment to engage functional networks synchronized to a given cognitive task.

The disruption of working memory networks in schizophrenia is still poorly understood. As reviewed in the preceding text, dynamic network connectivity is necessary for proper working memory functioning. Given the functional and anatomical "dysconnectivity" observed in schizophrenia (38), especially to the DLPFC (39), working memory deficits in schizophrenia could be due to dysfunction of establishing or changing brain networks. Thus, establishing a link between functional integration and working memory deficits is crucial to developing novel, neurobiological-based interventions to enhance working memory performance.

Current Treatments of Working Memory Deficits

Therapeutic strategies for working memory deficits in schizophrenia are of great interest, considering their predictive value for functional outcome. Nonpharmacological and pharmacological treatment strategies have been investigated but demonstrate mixed results.

Antipsychotic Treatment

Pharmacological studies have examined differences in effects of antipsychotic medications on cognitive functioning. Although showing small effects toward improved cognitive performance with treatment, some studies show therapeutic advantages of atypical antipsychotics compared with typical antipsychotics (40); however, the large, multisite CATIE trial (Clinical Antipsychotic Trials of Intervention Effectiveness) failed to find any advantage of atypical antipsychotics in treating cognition (1). Clozapine, the atypical antipsychotic agent for treatment resistant-schizophrenia (41), is no longer considered superior to other atypical antipsychotic agents for cognitive deficits (42). These results were driven by multiple pharmacological initiatives, such as the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) (43), TURNS (Treatment Units for Research on Neurocognition and Schizophrenia) (44), and CNTRICS (Cognitive Neuroscience Treatment Research to Improve Cognition Schizophrenia) (45). These initiatives highlight continuing interest and committed resources currently dedicated for novel therapies for cognitive deficits in schizophrenia and, in particular, working memory deficits. It should be noted that the long-term consequences of antipsychotic treatment might be detrimental to cognition. Progressive declines in working memory performance are observed in nonhuman primates undergoing chronic treatment of haloperidol over a 6-month period (46). Additionally, gray matter loss, higher neuronal density, and reduced glial cell number similar to that histologically observed in schizophrenia was reported in nonhuman primates exposed to olanzapine or haloperidol over a 2-year period (47,48). A longitudinal first-episode schizophrenia study showed progressive decline of white and gray matter volume correlating with antipsychotic medication dose (49). Thus, the evidence does not support a benefit from antipsychotic medication with regard to cognitive deficits but rather indicates a potential negative effect on working memory in schizophrenia during long-term treatment.

Pharmacological Targets

The pharmacology of working memory dysfunction might provide critical understanding for the development of new