Restoration of Cognitive Function with TDCS and Training in Serious Mental Illness
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SPECIFIC AIMS

Development of interventions that can effectively target and remediate the cognitive and functional impairment associated with serious mental illness has been aggressively pursued and is a treatment priority. Transcranial direct current stimulation (tDCS) is a safe, non-invasive neuromodulation technique that is capable of stimulating brain activity to facilitate learning. As such, it shows promise as an adjunctive technique that could potentiate the impact of cognitive remediation and enhance cognition and functioning in this patient population.

The primary objective of this study is to evaluate the pairing of two therapeutic techniques, cognitive remediation and tDCS, as a cognitively enhancing intervention. The efficacy of a cognitively enhancing intervention is critically dependent on its capacity to improve performance on untrained tasks assessing the same cognitive domain. In addition, it would be highly desirable if intervention-induced change also generalized a) to improve functioning on cognitive domains beyond those that are trained and b) to improve capacity to perform real-world cognitive demands. To address this objective, this study is designed to address the following questions. Is cognitive remediation paired with tDCS more efficacious than cognitive remediation delivered with sham stimulation? Is intervention-induced cognitive change sustainable?

Specific Aims.

Specific Aim 1: To examine the incremental benefit of pairing tDCS with cognitive remediation, we will enroll outpatients with schizophrenia, schizoaffective disorder, or bipolar I disorder to a double-blind, double-baseline, sham-controlled study. Working memory focused cognitive remediation concurrent with tDCS or sham will be administered for 48 sessions. We will examine efficacy of the intervention with change on:

a) novel versions of two working memory training tasks;
b) untrained measures that assess three domains of working memory performance – goal maintenance, capacity, and interference control (near generalization);
c) related cognitive constructs (far generalization);
d) functioning, measured in terms of capacity as well as community participation; and
e) symptom severity, measure in terms of overall symptom severity and severity of negative symptoms.

Hypothesis 1: We hypothesize that there will be an incremental benefit to augmenting working memory focused cognitive remediation with tDCS. Specifically, we predict that repeated administration of tDCS will produce 1) greater gains on novel versions of training tasks, 2) greater generalization of performance gains to conceptually similar (near transfer) and related cognitive processes (far transfer), 3) greater change in functioning, and 4) a larger reduction in symptom severity than working memory focused cognitive remediation administered with sham.

Specific Aim 2. The durability of intervention-induced changes in working memory, related cognitive domains, functional capacity, community functioning, and symptom severity will be examined in patients 6 weeks after working memory focused cognitive remediation with tDCS or sham. Hypothesis 2: We hypothesize that training gains achieved through pairing tDCS with working memory focused cognitive remediation will be maintained over time so that the predicted post-intervention between group difference in performance is sustained at 6 weeks post-intervention.

Achieving the proposed objectives will yield important information about the efficacy and durability of a novel pairing of cognitively enhancing interventions. Findings will inform treatment development with other cognitively compromised patient populations.

BACKGROUND AND SIGNIFICANCE

Despite pharmacological intervention, serious mental illnesses are among the leading causes of disability (1). This section will review the link between cognition and psychosocial functioning, highlight current efforts to address illness related cognitive impairments, and describe the development of cognitively enhancing interventions.

Cognition as a Treatment Target in Schizophrenia and Bipolar I Disorder. Research characterizing the nature of cognitive impairment in schizophrenia has established that cognitive impairment is: nearly ubiquitous; severe, compromising cognitive function by 1 to 1.75 standard deviations across a multitude of domains; relatively independent of clinical symptom severity; and predictive of clinically significant functional outcomes (2). Cognition in individuals with bipolar I disorder in an euthymic state has also been found to be impaired. The breadth and profile of neuropsychological changes is similar to that observed in schizophrenia and schizoaffective disorder, differing only in that the magnitude of impairment is less severe (118, 119). However, just as has been observed in schizophrenia, cognitive impairments associated with bipolar disorder have been found to contribute to poorer role functioning in the community (120). Community functioning (3), functional capacity (4, 5), and responsiveness to psychiatric rehabilitation (5) are all predicted by level of cognitive function, with cognitive performance often accounting for a greater proportion of the variance in functional outcomes than symptom severity (4, 5). Most importantly, when neurocognition has been found to change in the course of intervention, cognitive change has related to functional improvement, suggesting that cognitive change can potentiate functional change (6, 7).

Thus, development of new interventions that specifically address cognition has been ambitiously pursued. The mode of intervention that has shown the most potential is cognitive remediation, an intensive, behavioral intervention that engages cognitive processes through a highly structured learning experience. Restorative approaches to cognitive remediation aim to capitalize on neural plasticity, the brain's ability to alter it's structure, function, and connectivity in response to environmental demands (8). Treatment protocols are structured to provide repeated practice with tasks that target and exercise a cognitive function. Two meta-analyses concluded that intensive cognitive training (24-50 sessions) was capable of modifying cognition in patients with schizophrenia (9, 10). Few studies have examined the impact of cognitive training in individuals with bipolar disorder, however a recent, well-powered clinical trial found improvement in multiple cognitive domains (121). However, effect sizes in the meta-analyses for intervention-induced cognitive change were modest (d = .41-.45), and these estimates have become controversial. Methodological weaknesses common in the field might have contributed to an overestimate of treatment effects (11, 12). Among recent, methodologically strong, studies, several have reported medium to large performance gains on training tasks but have failed to find evidence of transfer to untrained tasks (11, 13-16), although there have been some successes (17, 18). At present, the inconsistency with which generalization occurs significantly limits the viability of cognitive remediation as an intervention for this population.

To establish that change in a cognitive function has occurred, evidence of transfer must be demonstrated through improved performance on an untrained task that uses unfamiliar stimuli and/or procedures to assess the same ability (near transfer) (19). The extent to which cognitive training generalizes to untrained tasks and related cognitive domains (near and far transfer) can be assessed with a focused training protocol. Our current understanding of neuroplasticity suggests that the most effective point of intervention is likely to be with a higher order cognitive process that is supported by a distributed neural network (19-21). According to the neuronal overlap hypothesis, focused training has the potential not only to restore the targeted cognitive function but also to enhance closely related cognitive functions (far transfer) that share common neural circuitry. Based upon these theoretical assumptions, working memory, a higher order cognitive process supported by neural circuitry spread throughout the dorsal lateral prefrontal cortex, the ventrolateral prefrontal cortex, anterior cingulate cortex, and thalamus (22), has become a primary treatment target.

Impact of Working Memory Training (WMT). WMT studies with healthy adults have examined behavioral and neural outcomes, and findings, while not robust, suggest that working memory is a modifiable cognitive function (23-26). Recent meta-analyses have revealed several meaningful trends in the literature. First, despite use of a variety of different WMT protocols, support was found for near transfer in verbal (d = .79) and nonverbal (d = .52) working memory domains in healthy adults (23). Furthermore, evidence of far transfer was found on measures of complex attention (d = .32) and nonverbal reasoning ability (d = .19) but not on abilities such as

verbal ability (d = .13), word decoding (d = .13), or arithmetic (d = .07). Finally, when specific types of WMT protocols were tested for evidence of transfer, training on complex span working memory tasks was related to transfer to complex attention tasks (24), while n-back training was linked to improvements in fluid intelligence (24, 25). Furthermore, imaging studies of healthy adults have found changes in regional brain activation (26), network connectivity (27), and increased perfusion (28) with WMT. These results suggest that working memory is modifiable and that enhancement can produce improved performance in related cognitive domains and enhanced neural readiness and efficiency.

Working Memory in Schizophrenia and Bipolar Disorder. Working memory is strongly related to intelligence and other higher order cognitive functions in both healthy adults and patients (29). Impairment in this domain has significant functional consequences for patients. Working memory performance is positively related to community functioning (30) and vocational status (31) and is predictive of functional recovery after an acute episode (3, 32). Patients with greater working memory ability make greater functional gains during participation in psychosocial rehabilitation (33) and are more likely to return to work (3) and to demonstrate greater interpersonal role functioning (32) one year after an acute episode. Studies indicate that patients and healthy individuals activate the same neural network when completing working memory tasks; however, the impaired performance observed in schizophrenia is associated with activation and connectivity abnormalities in the underlying neural circuitry (34)(122). Most notably, hypoactivation in the dorsal lateral prefrontal cortex has been observed during performance of working memory tasks, suggesting that patients have difficulty mobilizing neural resources for optimal task performance (34-36). In addition, patients appear less able to modulate connections between the dorsal lateral prefrontal cortex and other brain regions supporting working memory function (37)(123-124). These findings suggest that disruptions within and between regions of the neural network supporting working memory function contribute to its impairment in schizophrenia and bipolar disorder.

Modifiability of Working Memory in Serious Mental Illness. Only two published studies have examined the behavioral impact of WMT in patients with schizophrenia. In a poorly powered pilot study, transfer to an untrained verbal working memory task was found, while no group differences were found on a visual working memory task (38). In the second study, support was found for near transfer on a verbal working memory task (trend) and far transfer on an episodic memory task (significant). However, transfer to a more remote measure, global cognitive ability was not significant (39). To date, no studies have examined the behavioral impact of working memory training in patients with bipolar disorder. While there is a dearth of studies exploring the behavioral impact of WMT, imaging studies with patients with schizophrenia suggests that the neural network supporting working memory is modifiable. In a meta-analysis of imaging studies conducted in conjunction with WMT, both patients and healthy controls demonstrated changes in activation in multiple brain regions, suggesting that both groups have neural networks that are capable of change (26). Furthermore, in patients, change in neural activation has been associated with intervention-induced changes in working memory performance (40-43). Thus, imaging outcomes indicate that the underlying neural network is responsive to training.

Transcranial Direct Current Stimulation (tDCS) as an Intervention. TDCS is a non-invasive brain stimulation technique that can enhance cognitive performance by modulating neuro-excitability (44). Its primary mechanism of action is to shift resting membrane potentials in a polarity-dependent direction, with anodal stimulation typically increasing excitability. The mild stimulation delivered with tDCS does not induce action potentials, but rather, modulates spontaneous neuronal network activity. Thus, if the underlying neurocircuitry is capable of responding to stimulation, tDCS administration can facilitate neuroplasticity by changing the intensity and frequency of neuronal firing. TDCS is administered by placing two electrodes on the scalp, enabling stimulation to be targeted at specific neural regions. However, EEG and imaging studies have demonstrated that tDCS stimulation extends beyond the point of application to the entire neural network supporting a cognitive function (45, 46) as well as to functionally connected regions (47). TDCS administration has been found to be most effective when paired with cognitive training in healthy participants (48, 49). The proposed study aims to test the hypothesis that tDCS paired with WMT will enhance learning and generalization of training gains in patients with serious mental illness.

Repeated TDCS Administration in Healthy Adults. When tDCS or sham has been offered concurrent with very brief cognitive training protocols, four of the six studies found significant improvement post-intervention in tDCS but not sham conditions on tasks conceptually similar to the training tasks (50-55). Importantly, three of these studies examined the stability of tDCS-induced cognitive change and found support for its durability. Au et al. (53) reported that tDCS induced gains in working memory performance were maintained three months post-intervention, as measured by performance on a training task. Interestingly, Jones et al. failed to find a between-

group difference in performance gain post-intervention but found that the tDCS group maintained the training gains at a 1-month follow up, whereas the sham group did not (55). Most promisingly, Stephens and Berryhill (54) reported that 1-month post tDCS and WMT, significantly greater improvement on a measure of functional capacity was found in the tDCS condition. Given that training protocols of at least 32 sessions are recommended when cognitive training is offered alone (12), it is encouraging that significant and durable cognitive change is emerging within 10 sessions with the addition of tDCS. These findings suggest that tDCS could make a meaningful impact as a clinical intervention.

Repeated TDCS Administration in Patients with Serious Mental Illness. Only three published studies have examined the impact of repeated tDCS in patients with schizophrenia. Mondino et al. reported that patients receiving tDCS exhibited significantly fewer source monitoring errors after 10 sessions of tDCS (56). Unfortunately, no other aspects of cognition were assessed. In a study targeting the left dorsal lateral prefrontal cortex, investigators found that repeated administration of tDCS produced significantly greater cognitive improvement on measures of working memory, attention, and global cognitive function as compared to sham, with large effect sizes noted (d = 84. - 1.25) (57). Last, a case study examined two patients who received tDCS concurrent with 12 of 20 cognitive training sessions (58). Investigators reported moderate to large changes in multiple aspects of cognition in both participants, comparable to what is observed when cognitive training alone is offered for a much longer duration. Unfortunately, there was not a sham control, and therefore, performance gain due to tDCS could not be quantified. These findings suggest that tDCS can produce enhanced cognitive performance in schizophrenia. Presently, no study has examined tDCS combined with focused cognitive training to explore the impact of this paired approach on cognitive function and functional outcomes. Repeated administration has been studied to examine it's impact on depression and safety in patients with bipolar I disorder. Stimulation applied to the left dorsal lateral prefrontal cortex has been found to be safe and to reduce symptoms of depression (125, 126) Presently, well-powered randomized controlled trials are needed to assess the efficacy of this intervention in clinical populations (59).

Transfer of Working Memory Gains to Functional Outcomes. Development of cognitively enhancing interventions is motivated by the goal of reducing disability in schizophrenia. Recently, the results of two studies suggest that targeting working memory can have a measurable impact on functional outcomes (7, 60). Rispaud et al. (7) found that intervention-induced change in working memory and processing speed during a year of cognitive remediation was predictive of change in functioning, while changes in episodic memory and problem solving were unrelated to functional gains. Similarly, Subramaniam et al. (60) found that intervention induced change in working memory was predictive of vocational functioning at a six month follow up. Research suggests that transfer of cognitive gains to functional outcomes is facilitated by strategy training and opportunities to use cognitive skills with everyday activities (61). The addition of strategy training has been found to increase the impact of cognitive training on functional outcomes, d=.47 vs .34 (10), while action-based techniques that enable practice of cognitive skills in simulated environments has been found to produce significantly greater functional gains than cognitive training alone (62). Presently, the extent to which tDCS-induced cognitive gains can transfer to functional outcomes is unknown.

RESEARCH DESIGN AND METHODS

Participants will be randomized to a double-blind, double-baseline, sham controlled trial of a 48-session working memory focused cognitive remediation intervention paired with tDCS or sham. All participants who complete the 48-session intervention will be asked to return for follow up assessment 6 weeks post-intervention. A double-baseline design is being used to minimize measurement error, as the largest practice effects are observed between the first and second assessment. Given that very little is known about the durability of tDCS-induced change in cognition, the follow-up assessment will allow us to examine stability.

Participation in this study will be in addition to the clinical care that patients are receiving at study entry and will not replace psychiatric or case management services.

Data Collection. Participant Recruitment and Screening. Participants will be clinically stable outpatients between the age of 18 and 65 who meet DSM-5 criteria for schizophrenia, schizoaffective disorder, bipolar I disorder. Clinical stability is defined as not severely depressed or acutely manic and not having any hospitalizations or antipsychotic medication changes in the 4 weeks prior to enrollment. Establishing clinical

stability prior to study enrollment is necessary, as acute psychotic, depressive, or manic episodes or side effects due to recent medication changes could interfere with a participant's ability to complete the study protocol. Studies of patients with schizophrenia, schizoaffective disorder, and bipolar I disorder have found that these patients have very similar profiles of cognitive impairment, differing only in severity (63) (118). Therefore, patients with any of these diagnoses will be included in the study. In addition, given the ubiquitous nature of cognitive impairment in serious mental illness and our current lack of knowledge about who will respond to cognitive remediation, current research (64) and practice recommendations (65) are to offer the intervention to anyone with a diagnosis of schizophrenia, schizoaffective disorder, or bipolar I disorder Specific exclusion criteria will be: diagnosis of severe alcohol or substance use disorder in the last 6 months or mild alcohol or substance use disorder in the last month; history of a head injury or neurological disease that has compromised cognitive functioning; ability to speak English that is not sufficient to comprehend testing procedures; diagnosis of a learning disability, mental retardation, or a pervasive developmental disorder (premorbid IQ less than 75), diagnosis of a medical condition that is incompatible with tDCS procedures such as pregnancy, seizure disorder, eczema, metal or implants in their head, and open head wounds; participant does not demonstrate understanding of study procedures during consent process; participant has documented behavioral problems that prevent participation in a group intervention; and participation in a study of tDCS or cognitive remediation in the previous 12 months.

Patients will be recruited for the study in several ways. Dr. Nienow is a provider in Outpatient Mental Health at the Minneapolis VAHCS. She or a research staff person will meet with mental health staff to provide information about the study and to request that information be provided to appropriate patients. IRB approved descriptions of the study will also be included in the daily briefing to staff so that medical and mental health staff are aware of the study. Advertisements describing the study also will be posted at the VAHCS for potential participants to see. An IRB approved brochure and posters will be on display in the mental health clinics, in research kiosks in Building 70, and on the VA research website. Third, a waiver of consent for screening and a waiver of HIPAA authorization for screening purposes is being requested as part of this application. If approved, investigators will request a list of patients treated at the Minneapolis VAHCS who have a chart diagnosis and are within the age of participants eligible for this study. These individuals will be sent an IRB-approved letter that describes the study and that offers them the opportunity to indicate whether they would like to be provided with more information about it. Fourth, patients who have previously participated in research conducted by Dr. Nienow and who have expressed an interest in being contacted about future research will be sent an IRB-approved letter describing the study.

If a prospective participant expresses interest in the study after being approached through one of these means, a research staff person will provide him/her with more information about the study. If the individual continues to express interest, a brief, standardized, eligibility screening questionnaire will be completed. If the individual appears to be eligible, he/she will be scheduled for an in-person appointment and asked to provide consent for a diagnostic screening interview. At the time of scheduling, participants will be educated that there are risks to coming to a public space such as the VA during the COVID-19 pandemic, they will be told of the precautions taken by staff to minimize the risk of transmission during the screening session, and they will be provided with information about the types of safety practices they would be expected to abide by while on-site. If the participant continues to be interested, they will be scheduled for a screening session.

If after a diagnostic interview and a review of available medical records, the potential participant appears to be eligible for the study, he or she will be offered admission into the study. The consent form will contain a detailed description of all study procedures and possible risks and benefits of participation. Dr. Nienow or a trained research staff person will review the content of the form with the participant and will respond to any questions or concerns. The random assignment to cognitive remediation with tDCS or sham will be explained to participants. To ensure comprehension of the information provided in the consent form, participants will be asked a series of questions to assess their understanding.

Assessment. The assessment schedule is summarized in Table 1. The instruments administered at each assessment point are described below. The screening session will be 2 hours in length. Baseline, post-intervention, and follow up assessments will take approximately 5 hours to complete and will be divided into two 2 ½ hour sessions. Participants will be paid for their participation in all assessment sessions at a rate of $15/hour.

Diagnostic Screening Assessment (120 minutes). DSM-5 diagnosis will be established with the Structured Clinical Interview for Axis I Disorders (SCID-I) (66). Mood, psychosis, and substance use sections will be

administered. Participant self-report and available medical records will inform these ratings. As part of the diagnostic assessment, a psychosocial, medical, and psychiatric history interview will be completed. To ensure study eligibility, the Test of Premorbid Functioning (67) will be administered to obtain an estimate of premorbid intellectual ability. Last, a tDCS safety screen will be administered to identify existing medical conditions that are incompatible with tDCS (68)(115).

Table 1. Assessment Schedule

	Time				
Assessment Instrument	Screening Interview	Baseline	2nd Baseline	Post-Intervention (4-months)	6-wk Follow Up (5.5 months)
SCID-I/DSM-5 conversion	X				
Demographic Interview	X				
Test of Premorbid Functioning	X				
TDCS Safety Screen	X				
Number and Picture N-Back Tasks		X	X	X	X
Rotation and Reading Complex Span Tasks		X	X	X	X
Dot Pattern Expectancy Task		X	X	X	X
AX-Continuous Performance Task		X	X	X	X
Change Detection Task		X	X	X	X
Change Localization Task		X	X	X	X
MATRICS Consensus Cognitive Battery		X	X	X	X
University of California Performance-Based Skills Assessment-Brief		X	X	X	X
First Episode Social Functioning Scale (FE-SFS)		X	X	X	X
Brief Psychiatric Rating Scale		X	X	X	X
Brief Negative Symptom Scale		X	X	X	X

Cognitive, Functional, and Symptom Assessment. This set of assessment measures will be administered at baseline, post-intervention (4-month assessment), and at the follow up assessment (5.5-month assessment) to evaluate different degrees of skill transfer and cognitive generalization and to monitor symptom severity.

Symptom Assessment. The Brief Psychiatric Rating Scale (BPRS) (69) and the Brief Negative Symptom Scale BNSS) (105) will be administered to assess symptom severity in the previous week. With training, good reliability can be obtained on the BPRS and the BNSS with median ICCs of .81-.83 and .89-.95 being reported, respectively (70)(105).

Cognitive tasks administered as part of this assessment include: 1) novel versions of training tasks; 2) untrained working memory measures; and 3) measures of related cognitive constructs. As working memory is a multifaceted construct, and it is unknown whether components of this cognitive domain differ in malleability, near transfer measures were selected so that three distinct components of working memory – capacity, interference control, and goal maintenance could be assessed (71).

N-back task. This task measures executive processes in working memory and requires continuous monitoring, updating, and inhibition of irrelevant items to complete (72). This task presents participants with a series of stimuli that appear sequentially at the center of the computer screen for 500 ms with an inter-stimulus interval of 2000 ms. Participants are required to press one of two buttons identifying each stimulus as a target or a non-target, depending on whether it is a match to the stimulus two before it. Targets will occur on one-third of the trials. The task has demonstrated acceptable retest reliability (ICC = .80-.91), small practice effects (-.07 SD's), and little exposure to ceiling or floor effects (73). D prime, a performance indicator that controls for response bias, will be used to measure performance on this task.

Adaptable N-back tasks will be used as training tasks in the clinical trial. Non-adaptable, novel variants of the N-back tasks will be included in the assessment sessions. N-back tasks will be administered to assess transfer

on procedurally similar tasks with novel content.

Complex Span task. This task requires both memory storage and a manipulation processing requirement (74). Each trial starts with a memory item that is presented at the center of the computer screen for 500 ms. The memory items are followed by a distracter, presented in the center of the computer screen. The participant is asked to make a decision about the distracter (processing requirement) as quickly and accurately as possible. The distracter disappears after the participant's response, and the next memory item appears. After a few memory–decision sequences, participants are asked to recall the memoranda in correct serial order. The number of memory-decision sequences increases with each trial. Test-retest reliability has been reported to range from (ICC = .71-.90) across versions of the task (75). Performance is based upon the proportion of list elements recalled in correct serial order across trials.

Two adaptable versions of the complex span task will be used as training tasks in the clinical trial. Novel versions of these tasks will be administered in the assessment sessions so that transfer to novel versions of training tasks can be measured as well as impact of the intervention on the interference control component of working memory.

Dot Pattern Expectancy Task. This task was created to assess context processing deficits in patients with schizophrenia and is recognized as a measure of goal maintenance (76). In this continuous performance test the participant views a series of dot patterns that are presented sequentially in the middle of the computer screen. Participants must decide whether each stimulus is a target or a non-target, depending upon whether it was presented immediately after a to-be-remembered stimulus. The task has been found to have good internal consistency (alpha .70-.97), little exposure to ceiling effects, and good retest reliability (77). Performance will be assessed with d prime, a measure of sensitivity.

AX-Continuous Performance Task. This task is recognized as a measure of goal maintenance (106). In this continuous performance test, the participant views a series of letters that are presented sequentially in the middle of the computer screen. Participants must decide whether each stimulus is a target or non-target, depending upon whether it was presented immediately after a to-be-remember stimulus. This task is highly correlated with the Dot Pattern Expectancy Task (r = .65) but is easier to complete (107). Both tasks have been shortened and a composite measure will be made by combining d prime scores on these tasks into a single indicator of goal maintenance performance.

Change Detection Task. (78) In this task, a sample array of colored objects is presented to participants on a computer screen for 200 ms. After a 1,000 ms delay, a test array of colored objects is presented for 3000 ms. On 50% of the trials, the color of one of the items has changed between sample and test arrays. Participants are asked to indicate whether the sample and test arrays are the same or different. Performance across trials is measured with proportion correct, an index of the number of items that have been stored in working memory.

Change Localization Task. (79) In this task, a 5-item array of colored squares were equally spaced around an imaginary circle at the center of the screen. The array is presented for 500 ms. After a 1000 ms delay, the encoding array is followed by a test array. Participants use a mouse to click on the item that has changed to a different color. Performance across trials is measured with the proportion correct and is a measure of working memory capacity. Performance on change detection and localization tasks will be averaged to obtain the working memory capacity measure.

MATRICS Consensus Cognitive Battery (MCCB). This battery was developed specifically for clinical trials of cognitively enhancing agents developed for individuals with schizophrenia (80). The battery assesses 7 domains of cognition that have been identified as impaired in schizophrenia. All subtests have good test-retest reliability, ICC = .68-.85, relatively small practice effects d = .00-.22 across a 4-week interval, and little exposure to ceiling or floor effects (80). The MCCB assesses processing speed and reasoning. These domains may show improvement as a secondary effect of enhancing working memory, as working memory supports these cognitive processes (73, 74). The average of T-scores in these two domains will be the measures of far transfer.

Functional measures will be administered to assess functional capacity and community functioning.

University of California, San Diego Performance-Based Skills Assessment-Brief (UPSA-B). This measure of adaptive behavior will be used to assess skillfulness with activities of daily living (81). Participants are asked to complete brief role play tasks so that competence can be rated in two areas: finance and communication. The scores in these two domains are summed to obtain a total score. The UPSA has been validated for use with patients with schizophrenia and was found to have excellent inter-rater reliability (ICC = .91) and test-retest reliability across a 2-week interval, r = .93 (81). The brief version of this measure has been found to correlate r= .91 with the full measure (108).

First-Episode Social Functioning Scale (SFS). This self-report inventory will be used to assess functioning in the community in the prior 3-month period. This scale was developed for and validated with individuals with schizophrenia. Subscales assess independent living skills, interacting with people, social activities, intimacy, friendships, and family relations. Subscales have been found to have good internal consistency (alpha = .63-.80), to be sensitive to change, and without floor or ceiling effects (82). Subscales 1-5 on actual performance subscales will be summed to generate a total score.

Randomization. Group assignment will utilize a randomized block strategy, which is the preferred method of group assignment for small clinical trials of this nature (83). Accordingly, groups of 2 to 4 volunteers will be stratified into two groups so that patients assigned to each condition are equivalent in baseline N-back scores and age. We predict groups of this size will accumulate over 6-8 weeks of active recruitment. These stratified groups then will be assigned randomly to treatment conditions. The advantages of the randomized block strategy are that it maintains approximately equivalent group sizes throughout the trial, minimizes the confounding effects of initial differences (thereby decreasing reliance on statistical corrections such as ANCOVA), while at the same time preserving the interpretive strengths of unrestricted randomization.

Table 2. Training Session Protocol

Training Activity	Time (min)
TDCS/Sham Set Up	5
Lesson Planning	5
Cognitive Training	60
TDCS/Sham Equipment Removal	5
Bridging Activities	45
Total	120

Intervention. The working memory focused cognitive remediation intervention will consist of two components: focused cognitive training and bridging activities. Participants will attend 2-3 120-minute training sessions a week. A typical session protocol is presented in Table 2. To be considered a completer, a participant must complete 80% (39 sessions) of treatment. To maximize treatment completion, make-up times will be available each week. In addition, participants will receive payments for completion of treatment sessions. The payment scale increases by $1 after every 3 training sessions and ranges from $10 dollars per a session for the first 3 training sessions and $25 per a session for the last 3 training sessions.

Focused Cognitive Training. The cognitive training is computer-based and consists of approximately 15 adaptive computer exercises that place demands on working memory functions through verbal, visual, and spatial stimulus modalities. All tasks chosen for the intervention met the following criteria: 1) provide training in one or more working memory functions; 2) provide participant with ongoing feedback on performance; 3) allow task difficulty to be modified so that errors during training are minimized, 4) present novel stimuli, and 5) are appropriate for an adult patient population. The training tasks were selected from Happy Neuron software and experimental tasks used in research with patients with schizophrenia (40). The cognitive training intervention will be provided by a trainer in a 2 to 1 (participant to interventionist) ratio. The interventionist will provide instruction about the computer software, monitor participant progress, and facilitate engagement by rewarding effort and minimizing frustration. The interventionists will be Master's level psychology technicians supervised by Dr. Nienow. Participants will receive 48 hours of focused cognitive training, an amount consistent with dose recommendations for clinical trials of this nature (12).

Bridging Sessions: It has been recommended that bridging sessions provide metacognitive skills training that contains the following critical elements: identification of a highly valued personal goal; activities aimed to heighten awareness of cognitive strengths and weaknesses; explicit training in strategy use; training to plan, monitor, and evaluate task approach; and exploration of beliefs about individual abilities and situational challenges (61). All participants will participate in a 45-minute, group-based, bridging session immediately after the computerized cognitive training session. The curriculum for the bridging sessions will include each of these elements and be based on two manualized approaches that have been found to produce significant functional gains (62, 84), Compensatory Cognitive Training (84) and Action-Based Cognitive Remediation (62). Compensatory Cognitive Training provides education about cognitive difficulties associated with schizophrenia and teaches explicit

strategies for efficiently using attention, memory, prospective memory, and problem-solving skills. Action-based cognitive remediation builds on the intensive computerized cognitive training by pairing it with opportunities to apply cognitive skills in simulated real-world environments. Tasks are designed so that participants can immediately transfer the cognitive training to a tangible set of behaviors. This environment provides a platform for the therapist and group members to observe cognition in action and to discuss thoughts related to applying cognitive skills. In addition, both of these approaches place emphasis on setting individual goals that can be linked to the cognitive training.

Once every two weeks, an interventionist will meet with a participant individually, rather than in the group setting. These individual sessions will run concurrently with the group training, with one interventionist meeting with a participant individually and the other interventionist conducting the group-based training with the other participants. In the course of the 48-session training protocol, each participant will engage in 19.5 hours of group bridging activities and 4.5 hours of individual assessment and goal setting. The individual sessions will be used to establish and review progress toward goals.

Transcranial Direct Current Stimulation: TDCS will be administered with a StarStim neuromodulator. This device has been approved for use in research with an investigational device exemption due to meeting criteria for non-significant risk. Following the same procedures as were used during our pilot work, the current will be administered at 1 mA via two saline soaked electrode sponges (5 x 7 cm) for 20 minutes. The electrode placement will be based on the 10/20 EEG system. Specifically, the anodal electrode will be placed over F3 (left dorsal lateral prefrontal cortex) and the cathodal electrode will be placed in the contralateral supraorbital position. The neuromodulator can be programmed to offer tDCS or sham stimulation based upon a participant identification number that is programmed into the device. Thus, the device will administer either tDCS or sham stimulation, depending upon condition assignment, and neither the interventionist nor the participants will know the individual's assignment. Participants who are in the sham condition will receive 30 seconds of stimulation at the beginning of the session to mimic the experience of tDCS. This protocol has been found to be effective and is the recommended protocol for blinded tDCS administration (85).

Integration of Cognitive Training and TDCS. Adaptive versions of two integrative working memory tasks, the N-back and complex span tasks, will be trained on during every session. These tasks will be completed at the beginning of each session and will always be the training tasks used concurrent with tDCS or sham stimulation. These tasks were selected for training in conjunction with stimulation because: 1) they require the coordinated use of multiple working memory components, 2) have each been found to produce generalization, and 3) make independent contributions to the prediction of intelligence, suggesting a strong relationship with other higher order cognitive functions (72).

Study Blinds. To maximize the interpretability of any group differences that occur between the tDCS and sham conditions, multiple blinds will be in place. To equalize expectancy effects, patients will be blind to condition assignment. The StarStim neuromodulator will be used with all participants and is capable of offering a sham stimulation experience that is indistinguishable from tDCS. In addition, to minimize demand characteristics and differential provision of treatment, the interventionists who provide cognitive remediation will be blind to participant condition (tDCS vs sham). Furthermore, steps will be taken to blind the psychology technician who conducts the outcome assessments. Participants will be asked not to describe the intervention they are receiving to the psychology technician. In addition, the technician who conducts the outcome assessments will not provide the clinical intervention. The data collected will be coded in such a way that the investigator who conducts the data analysis will be blind to group membership.

Statistical Analysis Plan. T-tests will be conducted to determine whether important baseline variables are matched, such as working memory performance (N-back performance) and age. If any between-group differences emerge on these factors and they are found to relate to the dependent variables in any of the planned comparisons described below, the confounding variable will be added as a covariate of non-interest in the analysis.

Data Reduction: Consistent with recommendations that change in cognitive function be assessed with multiple measures of the construct (19), each working memory component will be assessed with two measures. Composite scores will be created by averaging the two measures of each aspect of working memory. Composite novel N-Back and novel complex span variables will represent performance on procedurally similar working

memory tasks with novel stimuli, composite scores on capacity, interference control, and goal maintenance tasks will reflect near transfer on untrained working memory measures, the MCCB Speed of Processing and Problem Solving and Reasoning composite will reflect far transfer to a related cognitive domain. Transfer to functional capacity and community functioning will be measured with performance on the UPSA-B Total score and the FE-SFS Total score. Impact on symptom severity will be assessed with the BPRS Total score and the BNSS Total score.

Data Analysis Plan for Aims 1 and 2: Cognitive and functional improvements are considered equally important outcomes for interventions targeting cognition (64). The primary measures of cognitive outcome for this study will be the capacity, interference control, and goal maintenance composites. These variables were selected as the primary outcomes, as near transfer must be demonstrated for an intervention to be deemed cognitively enhancing (19). The measure of functional capacity, the UPSA-B Total score, will be the primary functional outcome. This is consistent with the NIMH criterion that improvement on a measure of functional capacity must be demonstrated in addition to cognitive improvement for an intervention to be classified as cognitively enhancing (86). Thus, near transfer and change in functional capacity are the outcomes that have been deemed to be clinically meaningful. Mixed model approaches will be used, as they are well-suited to examining within subject change over time.

Specific Aim 1: Near and Far Transfer of Training. Mixed effect, repeated measure ANOVAs will be completed to test the hypotheses that WMT and tDCS will enhance performance significantly more than WMT and sham on 1) novel versions of trained tasks, 2) untrained working memory measures, 3) measure of related cognitive functions, 4) functional capacity, and 5) community functioning. Symptom severity is predicted to improve significantly more with WMT and tDCS than WMT and sham. Significant Group x Time interactions will allow rejection of the null hypothesis that WMT + tDCS offers no benefit as compared to sham.

Specific Aim 2: Durability of Cognitive and Functional Changes. To examine durability of near and far transfer and symptom change, mixed model repeated measure ANOVAs will be conducted. TDCS-induced cognitive change is expected to endure and post-intervention between group differences maintained.

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