Archival Report

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Increases in Intrinsic Thalamocortical Connectivity and Overall Cognition Following Cognitive Remediation in Chronic Schizophrenia

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ABSTRACT

BACKGROUND: Thalamic projections to the prefrontal cortex (PFC) are critical for cognition, and disruptions in these circuits are thought to underlie the pathophysiology of schizophrenia. Cognitive remediation training (REM) is a behavioral intervention that holds promise for improving cognition and functioning in schizophrenia; however, the extent to which it affects thalamo-prefrontal connections has not been researched. This study sought to determine whether patients with schizophrenia who undergo a placebo-controlled trial of REM show increased functional connectivity between the thalamus and PFC, and whether these changes correspond to improvements in cognition.

METHODS: Twenty-six patients with chronic schizophrenia were randomized to either 48 hours (over 16 weeks) of a drill-and-practice working memory–focused REM condition or an active placebo condition. All participants underwent cognitive assessment (MATRICS), as well as both resting and task-based functional magnetic resonance imaging before and after their respective intervention. All clinicians, technicians, and raters were blinded to participant condition.

RESULTS: We observed changes in resting-state connectivity in the PFC for the REM group but not for the placebo group. Increased intrinsic connectivity between the thalamus and right middle frontal gyrus correlated with improvements in overall cognition. Additionally, lower baseline cognition correlated with greater increases in connectivity between the thalamus and PFC. Similar findings were observed when patients were scanned during a working memory task.

CONCLUSIONS: These results suggest that increases in thalamo-prefrontal circuitry correspond with training-related improvements of the cognitive deficits associated with schizophrenia.

Keywords: Cognitive remediation, fMRI, Resting state, Schizophrenia, Thalamocortical connectivity, Working memory

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Schizophrenia is a chronic, debilitating mental illness characterized by neural dysconnectivity (1,2) and marked cognitive deficits (3,4). This disrupted connectivity has been observed to be widespread (5) and may underlie the heterogeneous symptom presentation within schizophrenia (6). While both prefrontal (7) and thalamic (8) disruptions have been identified in patients, a growing literature on resting-state functional connectivity has identified thalamocortical circuitry as particularly awry. Thalamic projections to the prefrontal cortex (PFC) show distinct patterns of connectivity in both animals and humans (9). Patients with schizophrenia have been shown to have reduced prefrontal-thalamic connectivity as well as hyperconnectivity between the thalamus and temporal, parietal, somatosensory/motor, and visual cortices (10–15). These findings are consistent with animal models and postmortem studies of schizophrenia (16). More recently, reduced prefrontal-thalamic connectivity has been found to not only correspond with cognitive impairment (17), but also predict conversion to psychosis among individuals at clinical high risk of psychosis (18). To our knowledge, no work has examined whether the deterioration of this circuit is reversible.

In the healthy brain, thalamo-prefrontal connections are thought to underlie critical aspects of cognition and consciousness (19,20), while disruptions in these neural pathways have been shown to be associated with cognitive dysfunction (21). For example, animal models have demonstrated that thalamo-prefrontal perturbations selectively disrupt working memory (WM) performance (22–24) and that WM training potentiates the functional synchronization of these regions (24). Thus, it is not surprising that structural and functional abnormalities within thalamo-prefrontal circuits are linked to overall cognitive impairments (17,25) and are thought to be an important treatment target in this population (26). If connections between the thalamus and areas such as the PFC are critical for patients' cognitive functioning, a useful next hypothesis to test is whether these abnormalities change with recovery.

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Basic research in behavioral neuroscience has established that the brain undergoes changes in organization and function in response to rehabilitative training (27), and these principles have been applied to treatments for cognitive dysfunction. Cognitive remediation training (REM) is an emerging class of behavioral treatments that aim to rehabilitate cognitive and psychosocial disruptions to facilitate psychiatric recovery in illnesses like schizophrenia. REM interventions typically consist of computerized training tasks that exercise a range of cognitive abilities, with the ultimate goal of generalizing improvements to untrained skills. REM for schizophrenia has demonstrated reliably modest improvements in cognition and psychosocial functioning (28,29), and emerging evidence suggests that neuroplastic changes may underlie these processes. Previous work has found that REM for schizophrenia supports neural changes during cognitive tasks (30,31) and rest (32). Recent work has demonstrated that prefrontal changes following REM reflected individual differences in improved WM (33) and meta-analysis suggests that both prefrontal and subcortical areas may become more active following REM in schizophrenia (34); however, it is unclear whether REM influences the connectivity between these regions.

The current study used a double-blind, placebo-controlled experimental manipulation of WM-focused REM to evaluate whether thalamocortical connectivity was affected by training, and how this might improve cognition. We first sought to determine whether the REM intervention increased intrinsic thalamocortical connectivity during rest in areas of the bilateral middle frontal gyrus and the anterior cingulate cortex (ACC), as these regions are associated with cognitive disruptions in chronic schizophrenia (35–37) and consistently show hypoconnectivity with the thalamus (10,12,17). Next, we examined whether changes in these circuits were linked to patients' cognitive improvements on domains beyond those for which they were trained. We then followed up on these analyses to determine whether cognition prior to training was related to neuroplastic changes in these thalamocortical circuits. To determine whether intrinsic thalamocortical connectivity at rest is similarly relevant to connectivity during cognitive demand, our final analyses examined whether these same relationships were observed during task engagement.

METHODS AND MATERIALS

Participants

Participants in the current study were recruited from a larger clinical trial examining REM (NCT00995553). All participants were required to have a DSM-IV diagnosis of schizophrenia or schizoaffective disorder, be between 18 and 60 years old, be clinically stable with no medication changes or hospitalizations in the previous four weeks, have a Wechsler Test of Adult Reading IQ score greater than 70, have no substance dependence in the last 6 months, have no substance abuse in the past month, have no history of serious head injury or neurological disorder compromising cognition, and show capacity to give consent.

Forty participants (of 81 engaged in the full clinical trial) consented to participate in the imaging study, which was approved by both the Minneapolis VA Health Care System and University of Minnesota Institutional Research Boards. Three participants were withdrawn prior to scanning after additional review of their medical history found them to be ineligible. Two additional participants were withdrawn due to inability to complete the scans. Six participants chose to withdraw because of lack of interest (n = 3) or anxiety in the scanner (n = 3). Data from three participants were lost due to experimenter error. No additional subjects were excluded for in-scanner movement (mean displacement threshold >2 mm). This left 26 participants in the current study. All had been randomized to undergo either 16 weeks of a WM-focused REM condition (n = 14) or a computer skills training (CST) placebo condition (n = 12). See Supplemental Figure S1 for study flow.

Training Procedure

Training took place at the Minneapolis VA Health Care System. Participants completed up to 48 hours of drill-and-practice–oriented training over 16 weeks (typically three 1-hour sessions weekly.). The REM and CST groups did not statistically differ with regard to the number of training hours (REM = 48.00 hours [SD = 0.00 hours], CST = 47.91 hours [SD = 0.28 hours]). Participants randomized into the REM condition completed a computer-based training program consisting of 21 adaptive exercises to place demands on WM in verbal, visual, and spatial modalities (see Supplemental Table S1 for the training curriculum). The tasks were selected from the Psychological Software Services CogRehab program (Psychological Software Services, Indianapolis, IN) and BrainTrain's educational software (Captain's Log MindPower Builder, BrainTrain, North Chesterfield, VA). Additionally, one-third of training time focused specifically on training with a version of the n-back task (0-, 2-, 3-, or 4-back). Participants were advanced to a higher n-back level after demonstrating mastery performance (85% accuracy) at the previous level across three consecutive task runs.

Participants in the CST condition participated in a course focusing on keyboarding skills and learning to use Microsoft Office 2007 (Microsoft Corp., Redmond, WA) for word processing, spreadsheet management, and presentation creation. The CST condition was designed to have the same level of training time, exposure to computers, and attention from treatment providers as the REM condition, but was devoid of any sort of drill-and-practice approach containing cognitive load.

Master- or bachelor-level interventionists facilitated both conditions and provided instruction, monitored progress, offered encouragement, and intervened to minimize frustration. Interventionists were unaware of the hypotheses being tested, and both interventionists and patients were told that the study was an examination of how two types of skills training impacted functioning in the community. Additionally, a doctoral-level clinician led weekly half-hour bridging sessions for both conditions. In these sessions, participants discussed their reactions to the training, skills they were learning, and how they might apply the skills in real-world situations.

Assessment Procedure

All enrolled participants underwent clinical, cognitive, and functional assessment at baseline and after 16 weeks of