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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

training. For the purposes of the current study, patients were assessed on the MATRICS Consensus Cognitive Battery (MCCB), which measures functioning in domains of attention, processing speed, WM, verbal learning, visual learning, reasoning, and social cognition (38). The dependent measure in the current investigation relied on the MCCB overall age- and gender-corrected *t* score.

### Imaging Procedure and Preprocessing

Patients underwent an 8-minute resting-state functional magnetic resonance imaging scan (320 scans) immediately after completing a word and picture *n*-back task (424 scans per task). The *n*-back tasks switched between 0-back and 2-back trials and were counterbalanced for whether the word or picture condition was given first. All images were collected at the University of Minnesota Center for Magnetic Resonance Research using a 3T Siemens Trio MRI scanner (Siemens, Erlangen, Germany) and a 32-channel head coil (repetition time = 1.5 seconds, echo time = 40 ms, flip angle = 90°, voxel size = 3.4 × 3.4 × 5-mm thickness, field of view = 22 cm, 35 axial slices). T1 reference images were also collected (voxel size = 1 × 1 × 1.2-mm thickness, 240 × 256 × 160 dimensions). Data were preprocessed using FSL (see http://www.fmrib.ox.ac.uk/fsl/). Images were spatially normalized in a 2-step procedure using rigid body transformations (FLIRT), where the images were first normalized to the individual structural image (in six directions), and then to the standard template (in 12 directions). Field maps were collected to carry out B0 unwarping, and motion correction used rigid body transformations (MCFLIRT) and a six-parameter motion regression. Scans were spatially smoothed at full width at half maximum of 7 mm, normalized using the mean volume intensity, and filtered with a high-pass frequency cutoff of 100 seconds. Mean average displacement (movement) across pre- and posttraining resting scans was 0.31 mm (SD = 0.40 mm) and 0.30 mm (SD = 0.33 mm) in the REM and CST groups, respectively. To maximize signal to noise in this randomized retest experiment, further data scrubbing was not conducted, and it was likely not indicated because group assignment was random, movement did not significantly differ as a function of time, group, or group by time (see Supplemental Table S2), and key comparisons were across-time change scores.

### Planned Analyses

A bilateral thalamus region of interest (ROI) was established using the Harvard-Oxford subcortical atlas and a conservative probability threshold of ≥50%. This was chosen to maximize the number of voxels located anatomically within the thalamus while minimizing those from neighboring brain areas. The ROI was then transformed into individual subject space using FSL's linear transformation tool (FLIRT). Individual subject time courses were extracted from the preprocessed data for each subject's thalamus ROI for both pre- and posttraining rest scans. The time course was then entered into individual-subject general linear models as a single regressor in FSL (similar to that of a psychophysiological interactions analysis) and contrasted within subjects to compare pre- and posttraining rest scans.

Following general linear model analyses, we performed voxelwise small-volume ROI analyses constrained to previously identified prefrontal thalamocortical disconnections (10) in the left middle frontal gyrus (LMFG), right middle frontal gyrus (RMFG), and ACC. All three ROIs were established with the Harvard-Oxford cortical atlas and thresholded in a conservative joint mask at ≥20% likelihood. Participants' duration of illness and Wechsler Test of Adult Reading IQ scores were included as covariates of noninterest in the model. Group images were cluster thresholded at $Z > 2.3$ and a within-mask significance threshold of $p = .05$ to maximize power for detecting changes within the a priori chosen ROIs. Voxels showing a significant group-by-time interaction in the small-volume group analysis were used as masks to extract individual subject connectivity values. Values were extracted at both time 1 and time 2 and were Fisher's *Z*-transformed before being entered into a repeated-measures analysis of variance to examine the magnitude and directionality of group-by-time interactions. We then correlated these *Z*-transformed values with change in overall cognition scores from the MCCB. We also assessed whether baseline MCCB overall score correlated with change in connectivity.

Last, we sought to conduct the above analysis in an *n*-back task to determine whether connectivity was modulated in response to WM demands. We focused our analysis on a picture *n*-back task that showed a clear behavioral effect of training, wherein patients in the REM group showed improved accuracy following training while those in the CST group did not (33). Using the same bilateral thalamus ROI, we extracted the time course from pre- and posttraining *n*-back scans. Time courses were then entered into a general linear model as psychophysiological interactions with the 2-back and 0-back conditions. At the group level, we again performed a voxelwise small-volume ROI analysis constrained to the same joint mask containing the LMFG, RMFG, and ACC regions. Group images were again cluster thresholded at $Z > 2.3$ and a within-mask significance threshold of $p = .05$. Last, we extracted and Fisher's *Z*-transformed individual β correlation values from significant voxels observed in the group analysis to examine the directionality of interactions and to examine correlations with MCCB scores.

## RESULTS

Participants in the two treatment groups did not differ on demographic, clinical, or cognitive measures at baseline (all *p*s > .12; see Table 1). Additionally, there were no differences on these variables between those participants included in the imaging study and those individuals who only participated in the clinical trial (all *p*s > .13). Baseline resting-state connectivity did not differ between groups in the ACC, LMFG, or RMFG ROIs (all *p*s > .55), and the test-retest reliability of these relationships in the active placebo group (CST) was found to be robust (ACC, LMFG, and RMFG intraclass correlation coefficients >.67), indicating reliable network connectivity between scans, mitigating the need for further data scrubbing procedures.

Voxelwise small-volume ROI analyses revealed differences between groups in the RMFG and ACC (Figure 1, Table 2). To clarify these observed relationships, we extracted and plotted

**Table 1. Pretreatment Group Demographics**

| | REM Condition ($n$ = 14) | CST Condition ($n$ = 12) | $t_{24}$ | $p$ |
|---|---|---|---|---|
| Age, Years | 42.93 (10.6) | 45.75 (7.7) | 0.8 | .43 |
| Education, Years | 13.47 (1.5) | 12.42 (1.04) | 1.2 | .24 |
| Parental Education, Years | 12.83 (4.3) | 13.21 (1.79) | 0.3 | .76 |
| WTAR IQ (Standard Score) | 104.00 (10.76) | 101.42 (11.56) | 0.6 | .56 |
| Duration of Illness, Years | 20.93 (12.73) | 18.5 (11.11) | 0.53 | .60 |
| Total CPZ | 551.80 (466.24) | 320.75 (280.81) | 1.6 | .12 |
| Baseline BPRS Total ($t$ Score) | 42.53 (9.74) | 45 (11.17) | 0.6 | .55 |
| Baseline MCCB Overall Score ($t$ Score) | 37.00 (16.34) | 34 (15.27) | 0.49 | .63 |

Values are mean (SD).

BPRS, Brief Psychiatric Rating Scale; CST, computer skills training; MCCB, MATRICS Consensus Cognitive Battery; REM, cognitive remediation training; Total CPZ, total chlorpromazine equivalents; WTAR IQ, Wechsler Test of Adult Reading IQ.

the β values from the significant voxels. Connectivity differences in the RMFG reflected a group-by-time interaction ($\eta^2$ = .35) driven by a significant pre versus post increase in the REM group ($t_{pre-post}$ = −3.10, $p$ = .009), and a trending but nonsignificant pre versus post decrease in the CST group ($t_{pre-post}$ = 2.14, $p$ = .06). A similar group-by-time interaction was observed in the ACC ($\eta^2$ = .29), driven by increased pre versus post connectivity in the REM group ($t_{pre-post}$ = −2.37, $p$ = .03), and a trend toward decreased pre versus post connectivity in the CST group ($t_{pre-post}$ = 2.04, $p$ = .07). No significant changes were observed in the LMFG.

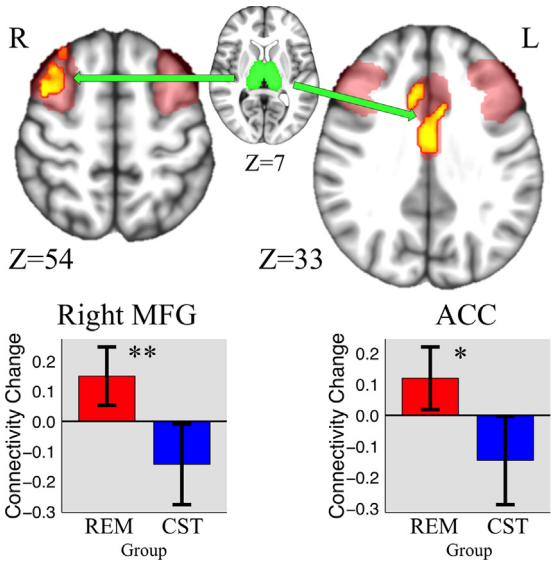


**Figure 1.** Group-by-time activation changes at rest. Green area denotes the thalamus region of interest. Transparent red areas denote the right middle frontal gyrus (MFG), left MFG, and anterior cingulate cortex (ACC) regions of interest. Hot areas denote increased activation from pre- to postintervention in cognitive remediation training (REM) > computer skills training (CST). Group-by-time interactions were observed in the right MFG and ACC, driven by increased thalamocortical connectivity following the REM intervention. Change in connectivity within each group is graphically depicted in the bar charts, where change (post > pre) reflected increases in connectivity in the REM group (red) but no significant changes in the CST group (blue). *$p$ < .05. **$p$ < .01. L, left; R, right.

Next we examined whether changes in the observed voxels were associated with training-related change in cognition. Increases in thalamus-RMFG connectivity were positively correlated with changes in overall MCCB score in the REM condition ($r$ = .55, $p_{uncorrected}$ = .043; Figure 2A) but not the CST condition ($r$ = .33, $p$ = .30), although this relationship did not interact with group. Additionally, we observed a trending negative relationship between baseline MCCB score and increased thalamus-RMFG connectivity in the REM condition ($r$ = −.53, $p_{uncorrected}$ = .05; Figure 2C), indicating a modest relationship between lower cognition scores at baseline and changes in intrinsic connectivity. Change in MCCB score did not significantly correlate with changes in connectivity in the ACC in the REM condition ($r$ = .18, $p_{uncorrected}$ = .54; Figure 2B), and again, this relationship was not observed in the CST condition ($r$ = −.11, $p$ = .72). However, lower baseline MCCB score in the REM condition trended with increased connectivity between the thalamus and ACC ($r$ = −.52, $p_{uncorrected}$ = .05; Figure 2D).

Last, we sought to determine whether these changes in intrinsic thalamocortical connectivity during rest were also present during task engagement. As illustrated in Figure 3, we observed connectivity changes during the task between the thalamus and ACC ($\eta^2$ = .39) driven by increased pre versus post connectivity in the REM group ($t_{pre-post}$ = −3.15, $p$ = .008) and decreased pre versus post connectivity in the CST group ($t_{pre-post}$ = 2.52, $p$ = .02). We also observed connectivity changes with the LMFG ($\eta^2$ = .34) driven by pre versus post increases in the REM group ($t_{pre-post}$ = −3.13, $p$ = .008), and a trending pre versus post decrease in the CST group ($t_{pre-post}$ = 2.04, $p$ = .07). No changes were observed in the RMFG. Notably, these changes were not observed in a psychophysiological interaction effect modulated by the 2-back condition, but rather were persistent across the duration of the task. This indicates that these differences are characterized by tonic changes in thalamo-prefrontal connectivity present during cognitive engagement. Also, changes in connectivity with neither the ACC nor the LMFG were predictive of changes in MCCB score or improvements in $n$-back task performance, but lower baseline MCCB score did show a trend-level correlation with change in connectivity with the ACC ($r$ = −.46, $p$ = .099).

**Table 2. Brain Areas Showing a Group-by-Time Interaction Reflecting Increased Connectivity During Rest and the *n*-Back Task**

| Region | Voxels | *Z*-Max | x | y | z |
|---|---|---|---|---|---|
| Connectivity During Rest | | | | | |
| ACC | 520 | 3.49 | 2 | –4 | 32 |
| | | 3.31 | 10 | 0 | 38 |
| | | 3.17 | 0 | 34 | 22 |
| | | 3.11 | –10 | 16 | 28 |
| | | 3.1 | –8 | 10 | 32 |
| | | 3.1 | 4 | 2 | 36 |
| RMFG | 460 | 4.19 | 42 | 4 | 54 |
| | | 3.75 | 38 | 4 | 58 |
| | | 3.24 | 30 | 30 | 46 |
| | | 3.16 | 26 | 28 | 38 |
| | | 3.15 | 40 | 28 | 46 |
| | | 3.1 | 30 | 0 | 64 |
| Connectivity During *n*-Back Task | | | | | |
| ACC | 494 | 4.18 | 6 | 4 | 36 |
| | | 3.98 | 2 | 0 | 36 |
| | | 3.41 | –2 | 2 | 34 |
| | | 3.38 | 10 | 12 | 42 |
| | | 3.37 | 4 | 14 | 44 |
| | | 2.97 | 4 | 6 | 26 |
| LMFG | 314 | 3.83 | –34 | 32 | 34 |
| | | 3.21 | –32 | 10 | 32 |
| | | 3.15 | –36 | 4 | 34 |
| | | 3.91 | –22 | 30 | 38 |
| | | 2.83 | –38 | 34 | 42 |

Group-by-time interaction reflects pre < post cognitive remediation training > computer skills training.

ACC, anterior cingulate cortex; LMFG, left middle frontal gyrus; RMFG, right middle frontal gyrus.

## DISCUSSION

The current findings suggest that one effect of REM in people with chronic schizophrenia is an increase in functional connectivity between the thalamus and various parts of the executive control network. Patients who underwent 16 weeks of a WM-focused drill-and-practice REM condition showed increased functional connectivity between the thalamus and both the RMFG and the ACC. This is notable given previous evidence for reductions in connectivity between these regions (10,13) and coincides with previous findings that demonstrate that REM influences structural connectivity in the thalamus (39). It also reinforces meta-analytic findings establishing thalamic and prefrontal areas as important neural targets for REM in schizophrenia (35) and offers a plausible mechanism by which these interventions may influence the brain's functional architecture. Specifically, focused cognitive training may induce neuroplastic changes evident at rest that reflect a core improvement in schizophrenia neuropathology observed in individuals vulnerable to psychosis (18) and across the illness's progression (10).

Additionally, increased thalamic-RMFG connectivity correlated with improvements in overall MCCB score, suggesting that plasticity in this circuit relates to training-related generalization to improve cognition. Few studies to date have demonstrated that changes in neural functioning from REM coincide with improvements on distal measures of overall cognition. This is especially relevant, as previous studies have established that disrupted structural and functional circuitry among the thalamus, PFC, and other subcortical regions underlie cognitive disruptions in schizophrenia (17,25). These preliminary findings, albeit in need of replication with more stringent statistical thresholds and larger samples, suggest that REM directly influences this mechanism to facilitate treatment-related remediation of the cognitive deficits prevalent in schizophrenia. Our findings also suggest that the REM generalized beyond the WM domain that was trained as a post hoc analysis demonstrated that the relationship between thalamic-RMFG connectivity and a general MCCB score without the WM domain remained robust ($r$ = .51, $p$ = .06).

We also demonstrated that lower baseline measures of cognition related to increased thalamocortical intrinsic connectivity following training in both the RMFG and ACC. This indicates that those individuals with poorer cognition before REM were those individuals that showed the most neural plasticity, potentially making them target candidates for this type of treatment. This is encouraging, as previous findings have identified individuals with higher baseline cognition as more responsive to REM interventions that target multiple cognitive domains (40). In contrast, other findings have shown that lower-functioning patients show more gains in response to functional skill–focused trainings (41) and REM combined with supported employment (42), which coincides with the current findings. In the present intervention, patients trained in a single cognitive domain: working memory. This focused training may have targeted disrupted neural pathways in lower functioning patients, enabling greater change in the underlying neuropathology.

The present findings demonstrated that changes in thalamocortical connectivity might also be present in the face of cognitive demands. However, rather than showing a modulatory effect (where connectivity might fluctuate during increased WM demand), we demonstrate that the ACC and LMFG showed tonic connectivity changes across the duration of an *n*-back task. This suggests that training-initiated changes may not only be present during rest, but also persist during cognitive engagement. These changes did not correlate with WM task improvement or changes on the MCCB, making it unclear whether this played a direct role in task approach or ability. Despite the lack of a behavioral correlation with these connectivity changes, this finding suggests that the previously observed intrinsic connectivity changes exist across cognitive states. It also remains unclear why we observed trending decreases in connectivity in the placebo condition during both task and rest, as they did not reflect changes in cognition in post hoc correlation analyses. Despite this, we continue to note that these observations do not discount the statistically significant increases in connectivity we observed in the REM condition.

A limitation of the current study is that we were constrained to an ROI approach, wherein we examined changes in hypothesis-driven brain areas of the PFC. In line with the findings of Anticevic *et al.* (10) and Atluri *et al.* (11), we also

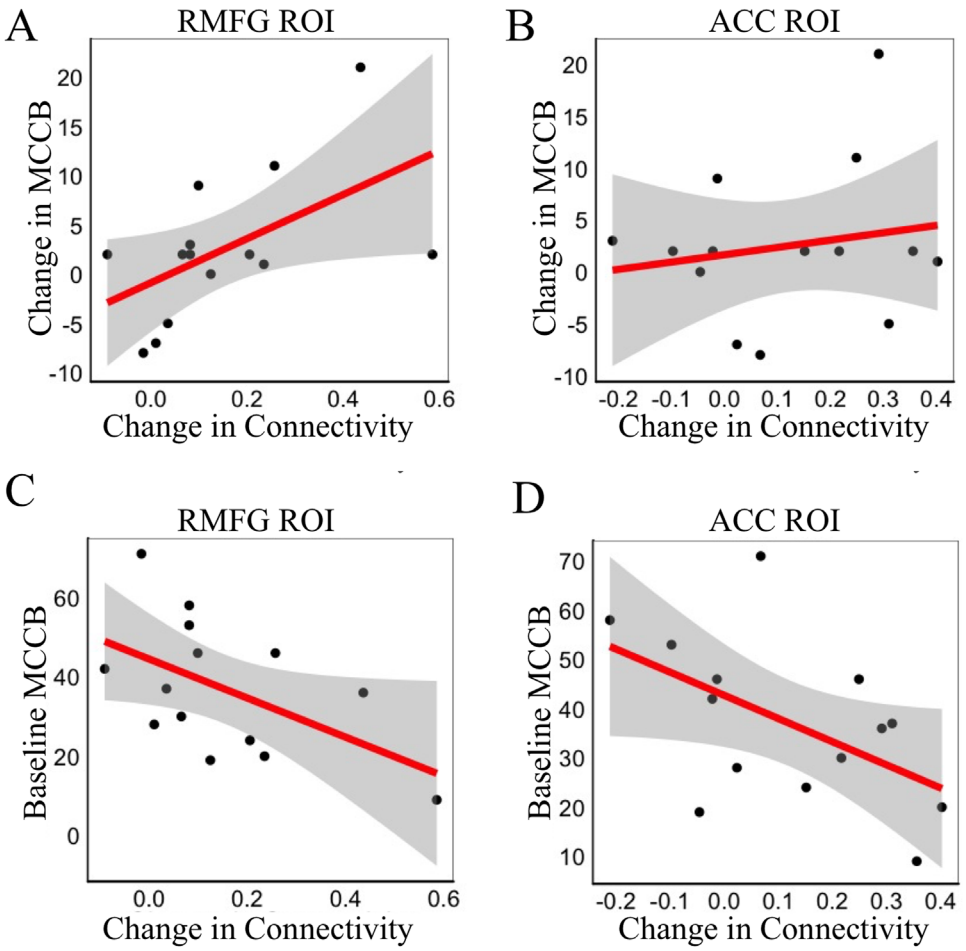


**Figure 2.** Correlations with MATRICS Consensus Cognitive Battery (MCCB). **(A)** Change in MCCB score significantly correlated with changes in connectivity with the right middle frontal gyrus (RMFG) ($r$ = .55, $p$ = .043). **(B)** However, change in MCCB score did not significantly correlate with changes in connectivity with the anterior cingulate cortex (ACC). **(C)** Baseline MCCB overall score negatively correlated with changes in connectivity with the RMFG ($r$ = –.53, $p$ = .05). **(D)** Baseline MCCB overall score negatively correlated with changes in connectivity with the ACC ($r$ = –.52, $p$ = .05). ROI, region of interest.

conducted post hoc analyses to examine whether REM influenced previously observed hyperconnections to parietal, somatosensory, and temporal areas, though no relationships were observed. Thalamocortical connections between these areas may be important to investigate in future studies, especially as they may coincide with recovery or alleviation of other types of psychiatric symptoms in schizophrenia. To date, it remains unclear whether differential changes to specific regions, even within the PFC, may reflect different aspects of recovery. Future studies may consider using a control group to functionally define thalamocortical ROIs and offer better specificity of relevant neural targets.

It is also not clear from the current findings whether WM-focused REM influences other neural circuits, in particular those that may connect via the thalamus. Studies in both humans and animals have highlighted the roles of thalamic, cortical, and striatal circuitry in WM function (22,23,25), and though the current study did not explicitly examine striatal connections, it offers a starting point for such investigations. The thalamus is a particularly complex neural region composed of subnuclei that project to various cortical structures. In particular, the dorsomedial nucleus may be especially important in thalamus-prefrontal connectivity, as it is well understood to have direct projections to the PFC (43). Future studies targeting connectivity from these subnuclei more specifically may offer a more nuanced understanding of the nature of REM-induced connectivity changes.

An important constraint of the current study is the sample size, and this likely limited our ability to show that the effects were robust when correcting for multiple comparisons (i.e., using a Bonferroni correction in multiple-correlation analyses). Though the current study has a sample size consistent with if not greater than previous imaging studies of REM (34), larger samples and replication in extant datasets will help to clarify the nature of thalamocortical connectivity and how REM or other psychiatric treatments may influence these networks. It will also be useful to understand in future studies whether changes in thalamocortical connectivity are durable and whether they coincide with improvements in long-term cognition and functioning.

We note that there are numerous approaches to examine thalamocortical connectivity; though our main findings trended in the same direction when adding additional nuisance variables to the model (i.e., signal from white matter and cerebrospinal fluid), future studies will be required to investigate whether this finding is robust across more rigorous

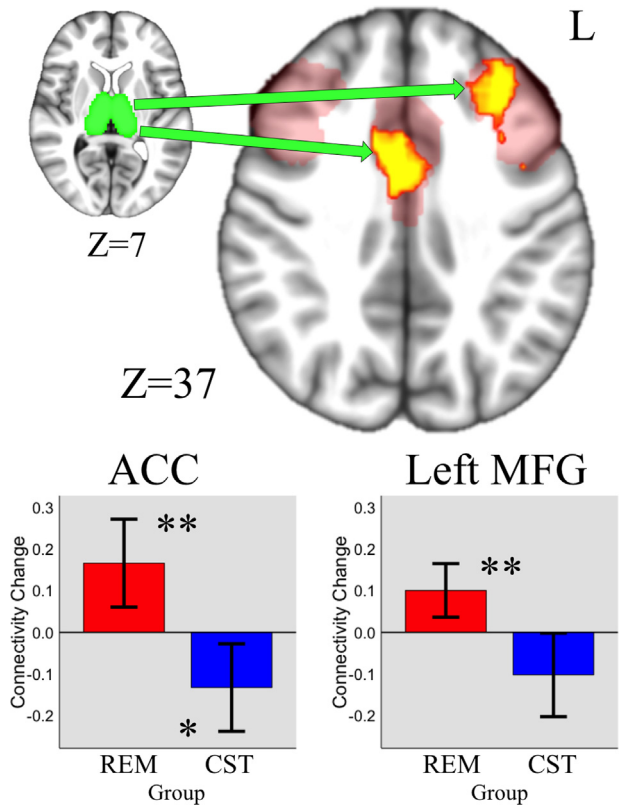


**Figure 3.** Group-by-time activation changes during the *n*-back task. Green area denotes the thalamus region of interest. Transparent red areas denote the right middle frontal gyrus (MFG), left MFG, and anterior cingulate cortex (ACC) regions of interest. Hot areas denote increased tonic activation (not modulated by the task) from pre- to postintervention in cognitive remediation training (REM) > computer skills training (CST). Group-by-time interactions were observed in the ACC and the LMFG, driven by increased connectivity following the REM intervention. Change in connectivity within each group is graphically depicted in the bar charts, where change (post > pre) reflected increases in connectivity in the REM group (red) and a decrease in connectivity in the ACC but not in the LMFG for the CST group (blue). *$p < .05$. **$p < .01$. L, left.

methodologies. Similarly, motion may be an especially pernicious confounder in studies of connectivity, and though not thought to be a factor in the current findings (see Supplemental Materials) will require careful consideration and control in future examinations of thalamocortical connectivity. It will also be important to replicate the current findings using more stringent statistical thresholds, especially in light of work suggesting that current methods may be vulnerable to false-positive findings (44).

The current study found that REM increased thalamocortical connectivity at rest and that this corresponded to improvements in overall cognitive functioning. Additionally, these changes persisted during task engagement and were related to lower pretreatment cognition. These findings offer a theoretical basis for the neural mechanisms supporting REM in schizophrenia and provide experimental support for animal and human findings that suggest that thalamocortical dysconnectivity is linked to cognitive dysfunction in schizophrenia.

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The authors report no biomedical financial interests or potential conflicts of interest.

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Commentary

Biological Psychiatry: CNNI

# Thalamocortical Functional Connectivity, Cognitive Impairment, and Cognitive Remediation in Schizophrenia

Neil D. Woodward

Neuropsychological impairment is common in schizophrenia and an important predictor of functional outcome. Cognitive deficits are believed to result from abnormalities in the structure, function, and connectivity of brain systems critical for normal cognition. Given the importance of cognition to functional outcome, there is tremendous interest in defining the neural mechanisms underlying neuropsychological impairment and developing interventions to ameliorate the deficits. The study by Ramsay *et al.* (1) in this issue of *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* is an important contribution to this effort. Using a double-blind, placebo-controlled experimental design, the authors examined the effect of approximately 48 hours of working memory–focused cognitive remediation training (REM) and computer skills training (CST) ("placebo" group) on thalamocortical functional connectivity measured using functional magnetic resonance imaging during the resting state and performance of an *n*-back working memory task. They found that thalamic connectivity with the middle frontal gyrus and anterior cingulate cortex improved significantly in the REM group compared with the CST group. Enhanced functional connectivity was detected during both resting-state and *n*-back working memory conditions. Moreover, within the REM group, enhanced prefrontal cortex (PFC)-thalamic connectivity correlated with improved cognition, as measured with the MATRICS Consensus Cognitive Battery, and negatively correlated with baseline cognitive performance, indicating that individuals with lower cognitive function at baseline exhibited greater improvement in functional connectivity.

The findings by Ramsay *et al.* (1) add to a growing literature implicating thalamocortical circuitry in the neuropathology of psychotic disorders and manifestation of cognitive impairment. The authors' rationale for examining the effect of REM on thalamocortical functional connectivity is based on the premise that thalamocortical circuits are 1) abnormal in schizophrenia and 2) related to the mechanisms of normal cognitive function and impaired cognition in schizophrenia. I explore these assumptions in this commentary, as closer inspection reveals important methodological issues and critical knowledge gaps that remain to be addressed.

The hypothesis that thalamocortical functional connectivity is abnormal in schizophrenia is well supported. Resting-state functional magnetic resonance imaging studies consistently find a combination of reduced PFC-thalamic connectivity and increased sensorimotor-thalamic connectivity in schizophrenia (2). This consistency, however, belies an important methodological hurdle to studies of thalamocortical connectivity. The first step in any connectivity analysis is to define the network or networks of interest. The "seed-based" approach that Ramsay *et al.* (1) used entails selecting a brain region (i.e., "seed") and calculating connectivity of the seed with either the rest of the brain or a region of interest, such as the PFC. In the case of thalamocortical connectivity, seed selection is complicated by the fact that the thalamus is a heterogeneous structure composed of several nuclei groups with distinct inputs and cortical connections that form parallel, largely segregated circuits. For example, the mediodorsal nucleus is densely interconnected to the PFC and critical for executive cognitive functions, whereas sensory relay nuclei, such as the lateral and medial geniculate nuclei, are connected almost exclusively to primary sensory cortices and critical for visual and auditory perception, respectively. Ramsay *et al.* chose to average the BOLD signal from the whole thalamus and calculate functional connectivity of the thalamus mean blood oxygen level–dependent (BOLD) signal with voxels in the middle frontal gyrus and anterior cingulate cortex regions of interest. Their decision to use the whole thalamus as a seed precludes an analysis of specific thalamocortical networks; this is a significant drawback given that their study is focused specifically on cognitive function and thalamic networks supporting working memory. The authors readily acknowledge this limitation. The reason why they chose this method is simple: the alternative approach, examining connectivity of specific thalamic nuclei, is difficult to implement. Commonly used structural neuroimaging scans lack the contrast to demarcate the boundaries of thalamic nuclei and/or the resolution to resolve smaller nuclei. Probabilistic diffusion tractography has been used to parcel the thalamus into subregions that correspond to specific nuclei groups (3). While an improvement over approaches that use the whole thalamus as a seed, connectivity-based segmentation of the thalamus is an indirect method for localizing thalamic nuclei. Ideally, specific nuclei could be directly visualized at the individual subject level. Significant progress has been made in developing novel anatomical imaging sequences capable of resolving individual nuclei (4). Such methods will be useful in the future for further clarifying the anatomy of thalamic dysconnectivity in schizophrenia and assessing the impact of behavioral and pharmacological interventions on specific thalamocortical networks (4).

The second premise of Ramsay *et al.* (1) that thalamocortical circuitry is critical for normal cognitive function and relevant to the mechanisms of cognitive impairment in schizophrenia is, broadly speaking, also well supported. Lesions to higher order nuclei, such as the mediodorsal nucleus, that are connected to association cortical areas impair cognition, and

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human neuroimaging has established that the thalamus is part of a superordinate PFC-cingulo-parietal "executive control" network that supports working memory and executive functions (5,6). Similarly, a meta-analysis of task-based functional imaging studies concluded that schizophrenia is associated with reduced activity in the thalamus during performance of executive function tasks (7). However, the relevance of BOLD functional connectivity to cognitive function is not nearly as well understood. It is often assumed that functional connectivity, measured during either resting state or task performance, is essential to cognition and that impaired cognition in schizophrenia is a consequence of dysconnectivity. However, data supporting these assumptions are surprisingly sparse. For example, relatively little is known about the relationship between individual differences in thalamocortical connectivity and executive cognitive abilities.

It is tempting to extrapolate findings from animal models linking PFC-mediodorsal nucleus beta-frequency coupling to the mechanisms of working memory to human functional imaging (8). However, we must "mind the translational gap" when doing so. The correspondence between functional coupling measured directly with intracerebral recordings and functional connectivity inferred based on the BOLD response is not completely understood. Uncovering the causal links between functional connectivity and cognition (for example, by examining the effects of repetitive transcranial magnetic stimulation–induced "virtual lesions" on connectivity and cognition) and determining if individual differences in connectivity biomarkers are associated with cognitive function will help clarify the relevance of functional connectivity to cognitive ability and cognitive impairment in schizophrenia. Critically, the fact that BOLD resting-state networks are conserved across species suggests that resting-state functional magnetic resonance imaging may be a useful translational tool for defining the mechanisms of normal and impaired cognition (9). Thus, while the results of Ramsay *et al.* fit nicely with animal studies, especially the finding that REM-induced change in connectivity correlates with improved cognitive function, more work is needed to determine if thalamocortical dysconnectivity is a useful biomarker of impaired cognition and/or treatment target for procognitive interventions.

Finally, I close this commentary with a brief discussion on the broader topic of REM clinical trials. There is considerable debate regarding the effectiveness of REM. A recent review of the literature on drill and practice "brain training" programs, such as those used by Ramsay *et al.* (1), concluded that 1) while there is abundant evidence that REM improves performance on the trained tasks, there is little evidence that training transfers to unrelated tasks, and 2) REM studies suffer from serious methodological limitations, including small sample sizes, open-label designs, and lack of "active" placebo condition (10). Encouragingly, Ramsay *et al.* show that cognitive improvements observed with REM working memory training extend beyond working memory–specific tasks included in the MATRICS Consensus Cognitive Battery, suggesting transfer of training effects. However, the selection of the appropriate placebo condition is especially important in REM trials and remains an area of debate. The ideal placebo condition should control for extraneous factors so that the "special sauce" of the treatment condition can be isolated. For behavioral interventions such as REM, this includes controlling for participant contact, expectation effects, and nonspecific improvements associated with drill and practice (e.g., nonspecific improvements in processing speed and arousal). CST, such as that used by Ramsay *et al.*, is commonly employed as a placebo control condition in REM studies. This raises the question: Is CST a good control condition for testing the efficacy of REM? CST likely controls for patient contact. However, it is not clear if it controls for expectation effects and general improvements in arousal and processing speed associated with drill and practice training programs. One solution to these issues may be to use comparative effectiveness designs that compare similar REM training programs that differ in the cognitive skills and putative neural circuits they ostensibly target (for example, comparing auditory vs. visual system training).

In summary, the study by Ramsay *et al.* represents an important and exciting early step in determining the impact of REM interventions on neural circuits in schizophrenia. Further work is needed, however, to refine the anatomical specificity of thalamic circuit abnormalities in schizophrenia and determine if thalamocortical connectivity is a useful biomarker of cognitive impairment and neural target of procognitive interventions.

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