

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

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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-mediiodorsal 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.

Acknowledgments and Disclosures

This work was supported by the National Institute of Mental Health Grant No. R01-MH102266.

The author reports no biomedical financial interests or potential conflicts of interest.

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Received and accepted Mar 21, 2017.

References

1. Ramsay IS, Nienow TM, MacDonald AW III (2017): Increases in intrinsic thalamocortical connectivity and overall cognition following cognitive remediation in chronic schizophrenia. *Biol Psychiatry Cogn Neurosci Neuroimaging* 2:355–362.
2. Giraldo-Chica M, Woodward ND (2016): Review of thalamocortical resting-state fMRI studies in schizophrenia. *Schizophr Res* 180:58–63.
3. Behrens TE, Johansen-Berg H, Woolrich MW, Smith SM, Wheeler-Kingshott CA, Boulby PA, *et al.* (2003): Non-invasive mapping of connections between human thalamus and cortex using diffusion imaging. *Nat Neurosci* 6:750–757.
4. Tourdias T, Saranathan M, Levesque IR, Su J, Rutt BK (2014): Visualization of intra-thalamic nuclei with optimized white-matter-nulled MPRAGE at 7T. *Neuroimage* 84:534–545.
5. Niendam TA, Laird AR, Ray KL, Dean YM, Glahn DC, Carter CS (2012): Meta-analytic evidence for a superordinate cognitive control network subserving diverse executive functions. *Cogn Affect Behav Neurosci* 12:241–268.

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6. De WL, Brouns R, Kavadias D, Engelborghs S, De Deyn PP, Marien P (2011): Cognitive, affective and behavioural disturbances following vascular thalamic lesions: A review. *Cortex* 47:273–319.
7. Minzenberg MJ, Laird AR, Thelen S, Carter CS, Glahn DC (2009): Meta-analysis of 41 functional neuroimaging studies of executive function in schizophrenia. *Arch Gen Psychiatry* 66:811–822.
8. Parnaudeau S, O'Neill PK, Bolkan SS, Ward RD, Abbas AI, Roth BL, *et al.* (2013): Inhibition of mediodorsal thalamus disrupts thalamofrontal connectivity and cognition. *Neuron* 77: 1151–1162.
9. Smucny J, Wylie KP, Tregellas JR (2014): Functional magnetic resonance imaging of intrinsic brain networks for translational drug discovery. *Trends Pharmacol Sci* 35:397–403.
10. Simons DJ, Boot WR, Charness N, Gathercole SE, Chabris CF, Hambrick DZ, *et al.* (2016): Do “brain-training” programs work? *Psychol Sci Public Interest* 17:103–186.