Prefrontal Cortical Abnormalities in Schizophrenia: A Validation via a Causal Neuromodulation Method

Ryan D. Webler and Ziad Nahas*

Department of Psychiatry, University of Minnesota, Minneapolis, MN, USA

*Corresponding author: Nahas Z, Department of Psychiatry, University of Minnesota, Minneapolis, MN, USA, E-mail: znahas@umn.edu


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Abstract

Neuroimaging studies have reliably detected prefrontal cortical abnormalities in schizophrenia. In a recent study, we built on these correlative findings using interleaved transcranial magnetic stimulation and functional magnetic resonance imaging (TMS-fMRI), a tool that enables simultaneous interrogation and imaging of discrete neural circuits and their connections. Compared to controls subjects with schizophrenia showed increased activation at the left dorsolateral prefrontal cortex stimulation site (BA9 and adjacent BA46) and decreased activation in contralateral right BA9 putatively indicative of impaired interhemispheric functional connectivity. In this mini-review, we discuss the implications of these findings and offer recommendations for how future studies can build on our results to shed novel light on the pathophysiology of schizophrenia.

Keywords: Schizophrenia; Neuromodulation; Abnormalities; Neuroimaging

Introduction

Schizophrenia is a chronic, disabling syndrome that is highly refractory to current treatment approaches [1,2]. Moreover, schizophrenia symptoms are heterogeneous [3] and fluctuate over time [4,5] complicating efforts to construct unified, testable disorder models that shed light on the etiology of schizophrenia and yield improved treatments.

Cognitive deficits and corresponding abnormalities in prefrontal cortical circuits have been detected in schizophrenia [6,7] and asymptomatic first-degree relatives [8]. These multimodal findings provide support for an intermediate ‘executive dysfunction’ schizophrenia endophenotype. Although neuroimaging studies have shed light on prefrontal cortical abnormalities in schizophrenia, these correlative findings require validation via causal neuromodulation methods [9].

Literature Review

Transcranial Magnetic Stimulation (TMS) is a safe, non-invasive form of neuromodulation that can excite or inhibit activity in discrete brain regions and their connections [10]. TMS interleaved with functional magnetic resonance imaging (TMS-fMRI) affords simultaneous brain stimulation and imaging [11] and can shed causal light on key affective disorder circuits [12]. Over the past two decades, our group has used interleaved TMS-fMRI to interrogate prefrontal cortical circuits in healthy and disordered populations to examine pharmacologically induced or disorder-related differences in effective connectivity [13-15].

Webler et al. [16] extended this work to schizophrenia, wherein we used interleaved TMS-fMRI to probe prefrontal cortical circuits in schizophrenia that have been implicated in executive dysfunction [7,17]. In addition to being the first study to use interleaved TMS-fMRI in a schizophrenia sample, schizophrenia participants (n=8) were unmedicated and controls (n=11) were well matched on key variables (e.g., race, sex, education, handedness, tobacco use)-significant methodological strengths that controlled for possible confounders [18,19]. To examine signal propagation in prefrontal cortical circuits, we stereotactically applied 35 triplet TMS pulses at 100 ms apart (10 Hz) to the left Dorsolateral Prefrontal Cortex (dPFC) at BA9. Stimulation was delivered while subjects performed a previously validated simple auditory Continuous Performance Task (CPT) [20], to ensure engagement and divert attention away from mild discomfort/noises associated with stimulation. Triplet pulse intensity was randomized across 0%, 80%, 100% and 120% of the adjusted resting motor threshold (rMT).

Discussion

Consistent with data from cognitive neuroimaging studies showing decreased prefrontal cortical inhibition in schizophrenia [21,22] we hypothesized that TMS would evoke enhanced activation at the BA9 target site and reduced activation in the contralateral right BA9 in participants with schizophrenia. As hypothesized, participants with schizophrenia showed increased TMS related activation at left BA9 and neighboring left BA46, and decreased right BA9 activation, compared to controls. Taken together, these findings implicate increased local “spill-over” and dysconnectivity between contralateral prefrontal circuits as pathogenic markers/mechanisms of schizophrenia. Because the blood-Oxygenated-Level-Dependent (BOLD) response is the summation of excitatory and inhibitory inputs, we could not distinguish whether ipsilateral BA9-BA46 spill-over in our study resulted from excitatory or inhibitory abnormalities. Future
studies pairing interleaved TMS-fMRI with pharmacological agents are necessary to adjudicate between these possibilities.

Although executive dysfunction is a relatively stable feature of schizophrenia [23], cognitive remediation therapies have been shown to yield small to medium effects on global function and cognition [24]. Interestingly, cognitive remediation treatment effects have been linked to prefrontal cortical functional and structural changes [25,26] including increased prefrontal cortical corpus collosom volume [27]. These results complement our findings of reduced contralateral effective connectivity in unmedicated schizophrenia and support the promise of mechanistic interventions that facilitate interhemispheric signal transfer. In a previous pharmacological TMS-fMRI study targeting the left dIPFC, we demonstrated that lamotrigine, a glutamatergic antagonist, reduced TMS induced left dIPFC activation and increased activation in functionally connected cortical and subcortical regions [15]. Whether lamotrigine or other pharmacological agents may yield similar effects in patients with schizophrenia remains an open and exciting question that warrants attention in future interleaved TMS-fMRI investigations.

Conclusion

Our findings implicate reduced interhemispheric signal transmission and hyperactivation in ipsilateral prefrontal cortical circuits in schizophrenia. Future studies should investigate whether reversing these abnormalities via biological and/or psychotherapeutic treatments may bolster the effects of clinical rTMS, which to date has not shown the capacity to remediate executive dysfunction in schizophrenia. Moreover, future interleaved TMS-fMRI studies should examine whether these abnormalities are present in first-degree asymptomatic relatives of patients with schizophrenia or pre-morbid individuals with high likelihood of developing schizophrenia. Additionally, future studies should include both TMS-fMRI and TMS-EEG in the same cohorts, or apply concurrent TMS-EEG-fMRI, to refine our understanding of excitatory and inhibitory imbalances in schizophrenia. Finally, there has been a great interest in using TMS as a treatment for auditory hallucinations. Studies using TMS-fMRI over temporal/auditory cortex could yield interesting clues on how to best optimize clinical outcomes.

References


(TMS) produces intensity-dependent bilateral effects as measured by interleaved BOLD fMRI. Biol Psychi 50: 712-720.


