Mini Review

iMedPub Journals
www.imedpub.com

Clinical Psychiatry
ISSN 2471-9854

2021
Vol.7 No. 2:87

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

Citation: Webler DR, Nahas Z (2021) Prefrontal Cortical Abnormalities in Schizophrenia: A Validation via a Causal Neuromodulation Method. Clin Psychiatry Vol.7 No. 2:87.

Received date: February 10, 2021; **Accepted date:** February 24, 2021; **Published date:** March 03, 2021

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 (dlPFC) 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 collosum 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 dlPFC, we demonstrated that lamotrigine, a glutamatergic antagonist, reduced TMS induced left dlPFC 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

1. Kennedy JL, Altar CA, Taylor DL, Degtiar I, Hornberger JC (2014) The social and economic burden of treatment-resistant schizophrenia: A systematic literature review. Int Clini Psychopharm 29: 63-76.
2. McCutcheon RA, Marques TR, Howes OD (2020) Schizophrenia-An overview. JAMA Psychi 77: 201-210.
3. Picardi A, Viroli C, Tarsitani L, Miglio R, Girolamo GD, et al. (2012) Heterogeneity and symptom structure of schizophrenia. Psychi Res 198: 386-394.
4. Millan MJ, Andrieux A, Bartzokis G, Cadenhead K, Dazzan P, et al. (2016) Altering the course of schizophrenia: Progress and perspectives. Nature Rev Drug Disc 15: 485.
5. Oorschot M, Lataster T, Thewissen V, Wichers M, Myin-Germeys I (2012) Mobile assessment in schizophrenia: A data-driven momentary approach. Schizophr Bull, 38: 405-413.
6. Guo J, Ragland JD, Carter CS (2019) Memory and cognition in schizophrenia. Molecular Psychi 24: 633-642.
7. Su TW, Lan TH, Hsu TW, Biswal BB, Tsai PJ, et al. (2013) Reduced neuro-integration from the dorsolateral prefrontal cortex to the whole brain and executive dysfunction in schizophrenia patients and their relatives. Schizophr Res 148: 50-58.
8. Li P, Fan TT, Zhao RJ, Han Y, Shi L, et al. (2017) Altered brain network connectivity as a potential endophenotype of schizophrenia. Sci Reports 7: 1-9.
9. Etkin A (2018) Addressing the causality gap in human psychiatric neuroscience. JAMA Psychi 75: 3-4.
10. Valero-Cabré A, Amengual JL, Stengel C, Pascual-Leone A, Coubard OA (2017) Transcranial magnetic stimulation in basic and clinical neuroscience: A comprehensive review of fundamental principles and novel insights. Neurosci Biobehav Rev 83: 381-404.
11. Bohning DE, Shastri A, Nahas Z, Lorberbaum JP, Andersen SW, et al. (1998) Echoplanar BOLD fMRI of brain activation induced by concurrent transcranial magnetic stimulation. Investi Radiol 33: 336-340.
12. Oathes DJ, Balderston NL, Kording KP, DeLuisi JA, Perez GM, et al. (2021) Combining transcranial magnetic stimulation with functional magnetic resonance imaging for probing and modulating neural circuits relevant to affective disorders. Wiley Interdis Rev: Cogn Sci: e1553.
13. Li X, Large CH, Ricci R, Taylor JJ, Nahas Z, et al. (2011) Using interleaved transcranial magnetic stimulation/functional magnetic resonance imaging (fMRI) and dynamic causal modeling to understand the discrete circuit specific changes of medications: Lamotrigine and valproic acid changes in motor or prefrontal effective connectivity. Psychi Res: Neuroimag 194: 141-148.
14. Li X, Nahas Z, Kozel FA, Anderson B, Bohning DE, et al. (2004) Acute left prefrontal transcranial magnetic stimulation in depressed patients is associated with immediately increased activity in prefrontal cortical as well as subcortical regions. Biol Psychi 55: 882-890.
15. Li X, Tenebäck CC, Nahas Z, Kozel FA, Large C, et al. (2004) Interleaved transcranial magnetic stimulation/functional MRI confirms that lamotrigine inhibits cortical excitability in healthy young men. Neuropsychopharm 29: 1395-1407.
16. Webler RD, Hamady C, Molnar C, Johnson K, Bonilha L, et al. (2020) Decreased interhemispheric connectivity and increased cortical excitability in unmedicated schizophrenia: A prefrontal interleaved TMS fMRI study. Brain Stimul 13: 1467-75.
17. Veelen NMV, Vink M, Ramsey NF, Kahn RS (2010) Left dorsolateral prefrontal cortex dysfunction in medication-naive schizophrenia. Schizophr Res 123: 22-29.
18. Abbott CC, Jaramillo A, Wilcox CE, Hamilton DA (2013) Antipsychotic drug effects in schizophrenia: A review of longitudinal FMRI investigations and neural interpretations. Curr Medi Chem 20: 428-437.
19. Schneider CE, White T, Hass J, Geisler D, Wallace SR, et al. (2014) Smoking status as a potential confounder in the study of brain structure in schizophrenia. J Psychi Res 50: 84-91.
20. Nahas Z, Lomarev M, Roberts DR, Shastri A, Lorberbaum JP, et al. (2001) Unilateral left prefrontal transcranial magnetic stimulation

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

21. Noda Y, Barr MS, Zomorrodi R, Cash RF, Farzan F, et al. (2017) Evaluation of short interval cortical inhibition and intracortical facilitation from the dorsolateral prefrontal cortex in patients with schizophrenia. Scient Rep 7: 1-12.
22. Radhu N, Jesus DDR, Ravindran LN, Zanjani A, Fitzgerald PB, et al. (2013) A meta-analysis of cortical inhibition and excitability using transcranial magnetic stimulation in psychiatric disorders. Clini Neurophysiol 124: 1309-20.
23. Shrivastava A, Johnston M, Shah N, Thakar M, Stitt L (2011) Persistent cognitive dysfunction despite clinical improvement in schizophrenia: A 10-year follow-up study. J Psychi Prac 17: 194-199.
24. Wykes T, Huddy V, Cellard C, McGurk SR, Czobor P (2011) A meta-analysis of cognitive remediation for schizophrenia: Methodology and effect sizes. Ameri J Psychi 168: 472-485.
25. Haut KM, Lim KO, MacDonald A (2010) Prefrontal cortical changes following cognitive training in patients with chronic schizophrenia: Effects of practice, generalization, and specificity. Neuropsychopharm 35: 1850-59.
26. Ramsay IS, MacDonald AW (2015) Brain correlates of cognitive remediation in schizophrenia: Activation likelihood analysis shows preliminary evidence of neural target engagement. Schizophr Bull 41: 1276-84.
27. Penadés R, Pujol N, Catalán R, Massana G, Rametti G, et al. (2013) Brain effects of cognitive remediation therapy in schizophrenia: A structural and functional neuroimaging study. Biol Psychi 73: 1015-23.