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Breakdown of Functional Connectivity in Cerebellar-Prefrontal Network Underlies Negative Symptoms in Schizophrenia

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Abstract

Objective: The interpretability of results in psychiatric neuroimaging is significantly limited by an overreliance on correlational relationships. Purely correlational studies cannot alone determine if behavior-imaging relationships are causal to illness, functionally compensatory processes, or purely epiphenomena. Here we take a two-step approach to identifying and then empirically testing a brain network model of schizophrenia symptoms. Negative symptoms (e.g. anhedonia, amotivation, and expressive deficits) are refractory to current medications and are one of the foremost causes of disability in this illness.

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Author Contributions:

MK and SME developed the BICEPS trial; AP-L, DO, LS and JDS developed the TMS trial. MAH and IG conducted the TMS trial; RB and MAH analyzed the data; RB and MAH wrote the manuscript with contributions from DO, JS, MK, AP-L.

Conflicts of interest:

DO: Served on Scientific Advisory Board for Neurocrine Inc in 2016 AP-L: Serves on the scientific advisory boards for Nexstim, Neuronix, Starlab Neuroscience, Neuroelectrics, and Neosync; and is listed as an inventor on several issued and pending patents on the real-time integration of transcranial magnetic stimulation with electroencephalography and magnetic resonance imaging.

JDS: Serves on the scientific advisory board for Cadent, consults with Biogen, Biohaven, and Pfizer, and holds the license with the General Hospital Corporation to the Brief Ataxia Rating Scale and the Cerebellar Cognitive Affective / Schmahmann Syndrome scale.

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Method: We used two-stage method: In the first cohort (n=44), we used a data-driven resting state functional connectivity analysis to identify a network whose connectivity corresponds to negative symptom severity. Then in a second cohort (n=11) we modulated this network connectivity with 5 days of twice daily transcranial magnetic stimulation to the cerebellar midline (vermis VIIb).

Results: A breakdown of connectivity in a specific dorsolateral prefrontal cortex to cerebellum network directly corresponds to negative symptom severity. Restoration of network connectivity with TMS corresponds to amelioration of negative symptoms, showing a strong relationship of functional connectivity change to negative symptom change (r=0.809,p=0003).

Conclusion: Our results demonstrate that a connectivity breakdown between the cerebellum and right dorsolateral prefrontal cortex is associated with negative symptom severity and that correction of this breakdown ameliorates negative symptom severity. Our results support a novel network hypothesis for medication refractory negative symptoms and indicates network manipulation may establish causal relationships between network markers and clinical phenomena.

Lay summary:

Human neuroimaging studies struggle to prove that discovered networks are causal to disease processes, and not epiphenomena. Here, we have used neuroimaging to find a surprising new network between frontal cortex and the cerebellum that is responsible for negative symptoms in schizophrenia. We then show with non-invasive brain stimulation that recovery of that network's function improves negative symptoms. This new model of network discovery combined with network validation shows promise in reversing symptoms of schizophrenia that are the most disabling and medication resistant.

Introduction

Identification of the brain network substrates of the symptoms of psychiatric illnesses has been a key goal of psychiatric neuroimaging. Numerous factors have confounded the discovery of brain circuits and networks dysfunction that cause symptoms and disability. Diagnostic heterogeneity, illness chronicity, technical limitations, and methodological differences have limited our ability to demonstrably identify the network basis of disabling psychiatric symptomatology(1).

Psychotic disorders such as schizophrenia are disabling, lifelong illnesses that afflict over three million people in the United States. A robust literature has examined how psychotic symptoms predict functional outcomes such as employment, social functioning, and independent housing. These studies have demonstrated that the most readily recognizable "positive symptoms" such as delusional thought and hallucinations are not the best predictors of functional status in individuals with psychosis. Rather, it is the severity of "negative symptoms" such as amotivation, expressive deficits, and anhedonia that best predict functional outcomes and overall quality of life (2, 3). The development of new interventions for these negative symptoms is hampered by a critical shortfall in our understanding of their pathophysiology, and our ability to modify the functional impact of

schizophrenia is further limited by the fact that psychotropic medications have limited efficacy in treating negative symptoms(4, 5).

Neuroimaging has the potential to illuminate the neuroanatomical basis of these deficits but existing studies have not converged on a consensus circuit or network target for amelioration in the clinic. Potential explanations for this non-convergence include methodological heterogeneity between studies(6), the effects of individual variance within a diagnosis (e.g. duration of illness(7)), or the possibility that multiple network pathology sub-types may present with similar clinical features (as suggested by Drysdale et al. for depression(8)). Even in scenarios where there is agreement between studies, most imaging studies are inherently correlational and cannot establish a causal relationship between imaging signal and the phenotype of interest, i.e. these findings may be causal to clinical manifestations of the illness, functionally compensatory processes, or purely epiphenomena. To address these concerns, there is a growing consensus that symptom-pathophysiology relationships may be best tested using a within-subjects design where pathophysiology is experimentally manipulated to determine the impact on symptomatology (9).

We propose therefore a strategy wherein a symptom-related circuit is empirically discovered, and then in a separate cohort, this circuit is challenged in a targeted way to assess causal relations(10). Recent advances in non-invasive brain stimulation have demonstrated the feasibility of manipulating single network connectivity(11) in a way that uniquely impacts the targeted network(12) and concurrently impacts behavior(13). This hypothesis predicts that if circuit pathology and psychiatric symptoms are causally linked, then it must follow that the manipulation of the circuit should be reflected in symptom modification.

In a cohort of participants with early-course schizophrenia/schizoaffective disorder, we sought to identify brain network correlates of negative symptoms. Methodological decisions included: 1) Recruitment of participants with early-course illness to mitigate the effects of illness chronicity, 2) Imaging processing tailored to mitigate movement effects, and 3) Analysis using an unbiased, data-driven approach to find symptom-imaging correlates at the individual voxel level. After identifying this network, in a separate, testing cohort, we examined the effect of repetitive brain stimulation at the network node most strongly associated with symptom severity. We show that a frontal-cerebellar circuit abnormality is associated with negative symptoms, and that non-invasive brain stimulation that modulates this circuit abnormality ameliorates negative symptoms, thus revealing a causal relation between the brain circuit abnormality and the clinical symptomatology.

Method

Participants

Network Discovery (Boston, Pittsburg): Data from forty-four participants with schizophrenia (n=35) or schizoaffective disorder (n=9) recruited for a clinical trial (NCT01561859) were included in the study. All participants provided written informed consent in accordance with the institutional review boards of the University of Pittsburg and Beth Israel Deaconess Medical Center prior to participation.

Network Validation (Boston): Data from eleven participants with schizophrenia recruited for a clinical trial (NCT01551979) were included in the study. All participants provided written informed consent in accordance with the institutional review board of Beth Israel Deaconess Medical Center.

MRI acquisition

Imaging was conducted on Siemens 3.0 T MRI systems. Briefly, $1mm^3$ T1 weighted anatomical scans were acquired, and multiple functional runs of approximately 6 minutes were acquired from all participants (124 time points, 3s TR, $3mm^3$ voxels).

MRI data processing

All analyses were pre-processed using DPABI image processing software (14). As a quality control metric, scans which exceeded motion thresholds (>3mm translation and/or >3° rotation) were discarded. Individual timepoints with framewise displacement > 0.5mm were discarded, and scans with >50% of volumes removed for framewise displacement were discarded. All data were preprocessed to remove motion (24-parameter), CSF signals, white matter signals, and an overall linear trend. A bandpass filter was applied (0.01–0.08Hz). Data were normalized with DARTEL into MNI space, and smoothed with a 8mm full-width half maximum kernel. Analysis was performed in a gray matter mask defined within the group.

Network identification was performed with multivariate distance matrix regression. Timecourses from regions identified with the network identification method were extracted with DPABI for the network validation cohort, and then correlated with z-transformed Pearson's correlation coefficients. Additional analysis was performed in SPM12 for voxelwise maps.

Clinical assessment

Participants were assessed with the Scale for Assessment of Negative Symptoms (SANS) in the Network Identification cohort, and by the Positive and Negative Symptom Scale (PANSS) for the network validation cohort.

Additional methodological details are indicated in supplemental information.

Results

Network Discovery With MDMR

Multivariate Dimension Matrix Regression reveals functional connectivity correlates of negative symptoms in schizophrenia—We examined clinical, demographic, and resting-state functional Magnetic Resonance Imaging (rsfMRI) scan data from 44 participants diagnosed with schizophrenia or schizoaffective disorder ("Network Discovery" in Supplemental Material). Negative symptom severity was quantified using trained raters administering a validated measure (The Scale for the Assessment of Negative Symptoms(15)). Preprocessing of rsfMRI data utilized procedures optimized to control for motion related effects(16). Individual fMRI scans were co-registered into a common space

(Montreal Neurological Institute). After preprocessing, rsfMRI data were analyzed using multivariate distance matrix regression (MDMR)(Figure 1a)(17). This approach allows for an unbiased, data-driven approach to determining functional connectivity. In contrast to most other approaches, MDMR allows quantification of how a variable of interest (here negative symptom severity) is reflected in the connectivity of individual voxels to the whole brain (i.e. at the finest resolution possible) without parcellating the brain into regions defined *a priori* (described in detail in Supplemental Material and Figure 1a). This approach has been used to examine the relationship between psychiatric pathology and connectivity(18–21). We modeled the impact of negative symptom severity on functional connectivity while covarying for effects of in-scanner motion, age, sex, study site, and prescribed medication dosage. This analysis identified the middle frontal gyrus (Brodmann Area 9) in the dorsolateral prefrontal cortex bilaterally in as the regions where functional connectivity covaried significantly with negative symptom severity. The right dorsolateral prefrontal cortex (peak voxel z-stat 3.82 at MNI coordinates: x36, y24, z30) demonstrated a more significant relationship between functional connectivity and negative symptom severity than the left (peak voxel z-stat 2.95 at MNI coordinates: x-33, y30, z42) (Figure 1b).

Negative symptom severity is inversely correlated with functional connectivity between right dorsolateral prefrontal cortex and the Default Mode Network— MDMR identifies brain regions where connectivity shows a significant relationship to a phenotypic variable of interest. *Post-hoc* testing is then necessary to determine the spatial distribution of that connectivity and the directionality of that connectivity. We calculated the subject-specific functional connectivity of the right dorsolateral prefrontal cortex region, and correlated these maps with negative symptom severity to identify the network that differentially connects to the dorsolateral prefrontal cortex depending on symptom severity. We observed that negative symptom severity is inversely correlated with right dorsolateral prefrontal cortex connectivity to a distributed brain network that includes both cerebral and cerebellar nodes of the so-called default network (22, 23) (Figure 1c). Notably, we found that within the default network, a connectivity breakdown between the right dorsolateral prefrontal cortex and the midline cerebellar node of the default network (MNI x-9, y-96, z-27) was the most significant predictor of negative symptom severity.

In summary, we have used a purely data-driven analysis to identify the most significant functional connectivity correlate of negative symptom severity in a schizophrenia sample. If disconnectivity between right dorsolateral prefrontal cortex and the cerebellum is *causally* related to negative symptom severity, then selectively reversing disconnectivity should be reflected in a reduction in negative symptom severity. We therefore sought to validate or refute a causal relationship between network disconnectivity and negative symptomatology.

Network Validation with TMS

Empirically testing the causal relationship between network connectivity and negative symptom severity—We and others have previously demonstrated that repetitive transcranial magnetic stimulation (rTMS) can selectively modulate network functional connectivity in healthy participants (11, 12, 24). We hypothesized that if breakdown in dorsolateral prefrontal cortex connectivity is causally linked to negative

symptom severity, directional rTMS restoration of functional connectivity should be reflected in amelioration of negative symptom severity.

The most significant relationship between disconnectivity and symptom severity is between the right dorsolateral prefrontal cortex and midline cerebellum. We therefore studied an independent, testing cohort of participants with schizophrenia who underwent an interventional, sham-controlled trial of rTMS that targeted the cerebellar vermis (midline) (n=11, see Network Validation in Supplemental Materials; Figure 2a). Participants underwent clinical characterization by a trained rater blinded to treatment condition. Negative symptom severity was quantified using a commonly used and validated scale (the Positive and Negative Syndrome Scale (PANSS) negative symptom subscore(25). Participants underwent a baseline resting state fMRI scan and then were randomized to either active or sham rTMS modulation of the cerebellum. Intermittent theta burst (10 bursts of three biphasic pulses at 50 Hz, repeated at 5 Hz, for 10 seconds for a total of 600 pulses) of 100% of active motor threshold was applied to the midline cerebellum. Sham electrodes were placed on all subjects at the neckline. Blinding codes were used to determine which side of an active/passive Magpro coil (cool B65 A/P, Magventure A/S, Denmark) was used for stimulation.

Participants underwent two rTMS sessions per day separated by 4 hours for five days. This intensity, frequency, and duration of stimulation was chosen on the basis of demonstrated efficacy in ameliorating negative symptoms at the group level(26). After this week of repetitive stimulation, subjects underwent clinical characterization and a follow-up resting-state fMRI scan (Figure 2a). We hypothesized that rTMS induced change in functional connectivity and change in negative symptom severity should be correlated for all participants (i.e. regardless of sham versus real stimulation). Specifically, an increase in cerebellar-dorsolateral prefrontal cortex connectivity should be reflected by a reduction in symptom severity.

Reversing cerebellar-dorsolateral prefrontal cortex disconnectivity ameliorates negative symptom severity.—We measured pre-trial versus post-trial, within-subject change in negative symptom severity as well as change in functional connectivity between the right dorsolateral prefrontal cortex and the cerebellar node of the default network. As predicted, we observed a strong and significant (r= −.809, p=.003, 95% CI: −0.948, −0.405) relationship between increased connectivity and reduction in symptom severity (Figure 2b).

Testing distributed network versus cerebellar specific effects on negative symptoms—Consistent with our original hypothesis, we observed that selectively increasing functional connectivity between the cerebellar node of the default network and the right dorsolateral prefrontal cortex results in reduced negative symptom severity. We sought to determine if this effect is mediated solely by changes in cerebellar-dorsolateral prefrontal cortex connectivity or is the result of cerebellar rTMS increasing functional connectivity broadly between the right dorsolateral prefrontal cortex and the rest of the default mode network i.e. both cerebellar *and* cerebral nodes. We tested these possibilities by generating whole-brain maps of change in functional connectivity (pre-versus post-rTMS) to

the right dorsolateral prefrontal cortex for each patient. We then regressed these maps against individual change in negative symptom scores to determine where connectivity change correlated with symptom change. This whole brain analysis identified one area where connectivity change corresponded to symptomatic change: The cerebellum at the level of rTMS stimulation (p<.001). In this region the correlation between symptomatic improvement and connectivity change was particularly strong (r=−.952, 95% CI: −0.987, −0.821). The cerebral nodes of the default network were not identified by this analysis even at lower threshold (p<.05) (Figure 3). This suggests that in our trial, symptomatic improvement across all participants is mediated by rescue of cerebellar-dorsolateral prefrontal cortex functional connectivity rather than a more broad modulation of multiple cerebral networks, as would be expected if this network connectivity mediates negative symptoms.

We also found that the active stimulation condition was significantly more effective than sham at increasing cerebellar-dorsolateral prefrontal cortex connectivity (t (8.96) = 2.938, p = .017) and reducing negative symptom severity (t (7.99) = 2.931, p = .019).

In summary, we have used a combination of resting-state fMRI imaging and multivariate data analysis to discover a dorsolateral prefrontal cortex-default network connectivity breakdown related to schizophrenia negative symptom severity. This connectivity breakdown is strongest between dorsolateral prefrontal cortex and midline cerebellum. When repeated rTMS stimulation is used to selectively rescue cerebellar-dorsolateral prefrontal cortex connectivity, negative symptom severity is ameliorated.

Discussion

The ability to use biology to differentiate phenotype and prognosis has improved greatly in recent years, but most studies to date have not been structured to answer questions about the causal relationship between biomarker and behavioral phenotype. This inability to differentiate the biology that mediates disease from compensatory processes or obligatory epiphenomena has led to a “causality gap in human psychiatric neuroscience” (27). In addition to limiting our understanding of the basic neuroscience of psychiatric illness, the absence of a biological target that mediates disease state means that even large trials that evaluate symptomatic response to an intervention cannot lead to a greater understanding of why some patients respond and others do not.

Here we have combined two mature technologies for neuroscience discovery (resting-state fMRI and rTMS) and applied them to better understand disabling, medication refractory symptoms of schizophrenia. Using recent developments in data-driven imaging data analysis, we have identified a network biomarker of negative symptom severity in a cohort of participants. We then tested the causal nature of this network dysfunction through the selective modulation of this network in a trial designed to hold other factors constant (i.e. a within-subject design). We observed that changing cerebellar-dorsolateral prefrontal cortex connectivity appears to reverse the experiential and expressive deficits referred to as negative symptoms. This finding provides empirical support for a causal relationship between dysfunctional connectivity and psychopathology.

Our findings suggest the existence of at least one network circuit linked directly to negative symptoms. Investigators using alternative approaches have identified different network-symptom relationships(28–30). We suspect that the network we identify here is present within those datasets, but it may be obfuscated by common confounds in psychiatric neuroimaging such as diagnostic heterogeneity, duration of illness, and technical considerations including motion in the scanner. Notably, although our network discovery dataset consisted of early course (<8 years since diagnosis) schizophrenia participants, we were able to validate this symptom-connectivity relationship even in participants with later course illness. This suggests a consistent network-symptom relationship that may be inconsistently observed in purely imaging studies.

There are some existing preliminary hypotheses regarding the emergence of negative symptoms from cerebellar-dorsolateral prefrontal cortex connectivity. Prior imaging studies have identified frontal abnormalities in schizophrenia patients that may be associated with negative symptoms (31, 32). What is the significance of identifying the dorsolateral prefrontal cortex as one node of a circuit that includes the cerebellum? Our findings may be seen as consistent with a dysmetria of thought theory(33–35) which hypothesizes that just as the cerebellum regulates the rate, rhythm, force and the accuracy of movements, so does it regulate the speed, consistency, capacity, and appropriateness of mental or cognitive processes, including those subserved by the prefrontal cortex. It had been hypothesized that cerebellar dysfunction could underlie the pathophysiology of schizophrenia (36–41) but this had not been demonstrated until now.

In sum, the precise localization of a prefrontal-cerebellar network is critical for identifying the underlying neural substrates of the disabling negative symptoms of schizophrenia. Our results provide experimental evidence in support for such a circuit, which, when directly modulated, rescues these deficits.

Our results are consistent with a potentially reproducible model of TMS based rescue of a breakdown of connectivity. Two prior studies demonstrated a similar reduction of negative symptoms at the group level after ten sessions of intermittent theta burst stimulation to cerebellar vermis (26, 42). Unfortunately, although these studies produced potential therapeutic improvement, they provided no mechanistic explanation of how improvement occurred, nor did they demonstrate that improvement was due to correction of existing circuit pathology. Taken together with the present data, it suggests an effect that is readily replicable. Furthermore, our network identification sample and TMS sample were collected at different facilities, which is reassuring about the generalizability of our results.

The strengths of this study include: 1) It establishes a causal relationship between resting-state functional connectivity and disease expression in a psychiatric illness, moving the field away from purely correlational studies. 2) It establishes functional connectivity between dorsolateral prefrontal cortex and the cerebellum as a quantifiable *and engageable* target that modulates disabling, medication-refractory negative symptoms in schizophrenia. 3) It is a model for how a precision medicine approach (i.e. targeting disease specific pathophysiology to change clinically observable symptomatology) may be applied to psychiatric disorders. 4) By linking neuromodulation to a biological outcome (functional

connectivity) rather than symptomatic response alone, this model allows *individual level* explanation of response and non-response to rTMS.

Limitations of the current study include the limited sample size in the network validation (TMS) experiment. In a traditional rTMS clinical trial with clinical response as the only readout of TMS engagement, our sample size would be inadequate to make conclusions about the cerebellum's role in negative symptoms. By marrying clinical response with functional connectivity, we were more than sufficiently powered to discover the strong relationships between connectivity and symptomatology. With a larger sample size, we could address questions about what factors mediate connectivity change (and therefore symptom change) in response to rTMS e.g. Do individual differences in duration of illness and network topography modulate connectivity change to a course of rTMS? Assessments of blinding for all participants from raters and participants were not available for the present study, which may be helpful in future studies to assess placebo response.

Finally, while our findings demonstrate a target biological substrate for the treatment of negative symptoms, we do not imply that cerebellar-targeted TMS is the sole intervention which can do so. Our ability to measure cerebellar-dorsolateral prefrontal cortex circuit integrity using fMRI imaging suggests that functional connectivity may be a useful marker of efficacy on negative symptoms for other therapeutic interventions, independent of rater assessment. Similarly, previous TMS studies have not systematically investigated stimulation parameters, and it is therefore plausible that our connectivity assessment may be useful as a direct measure for rapid protocol development.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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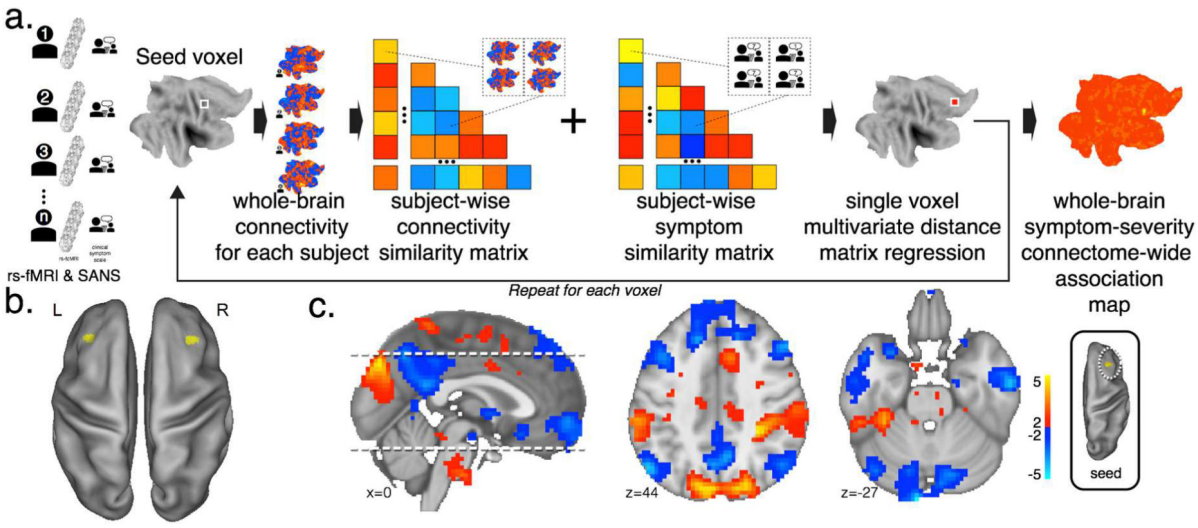

Figure 1.

Multivariate distance matrix regression (MDMR) of negative symptoms in schizophrenia. (a) The MDMR method (after Shezad et al.[16]). Symptom scales and resting state fMRI data is collected from each participant. For each voxel in the brain atlas: the voxel is used as a seed region to create a connectivity map for each participant. Those maps are compared to each other to create a subject-wise similarity matrix. The symptom scale scores for each participant are then combined with the connectivity similarity matrix to produce a pseudo-F statistic which describes the symptom predictor's ability to describe the similarity of the functional connectivity. A permutation test of the subject labels can be used to test the significance of this pseudo-F statistic. Each MDMR voxel wise result is then combined to produce a map of each voxels' connectivity pattern's ability to predict a symptom score. (b) MDMR results for negative symptoms in the network discovery cohort, voxelwise thresholded $p<.005$, cluster corrected at $p<0.05$. Bilateral dorso-lateral prefrontal cortex regions are identified. (c) MDMR results demonstrate the locations where the variability in connectivity from that region co-varies with symptom scales. In a post-hoc analysis, a seed-region was placed in the right dorsolateral prefrontal cortex in all subjects and then this seed-based connectivity map was correlated with symptom severity to identify locations where increasing connectivity to dorsolateral prefrontal cortex corresponds to better symptoms (red) and decreased connectivity corresponds to worse symptoms (blue). Thus, regions in blue correspond to locations where connectivity breakdown with dorsolateral prefrontal cortex corresponds to symptom worsening. The strongest dorsolateral prefrontal cortex connectivity breakdown to symptom severity correlation was observed in the midline cerebellum (MNI x-9, y-96, z-27).

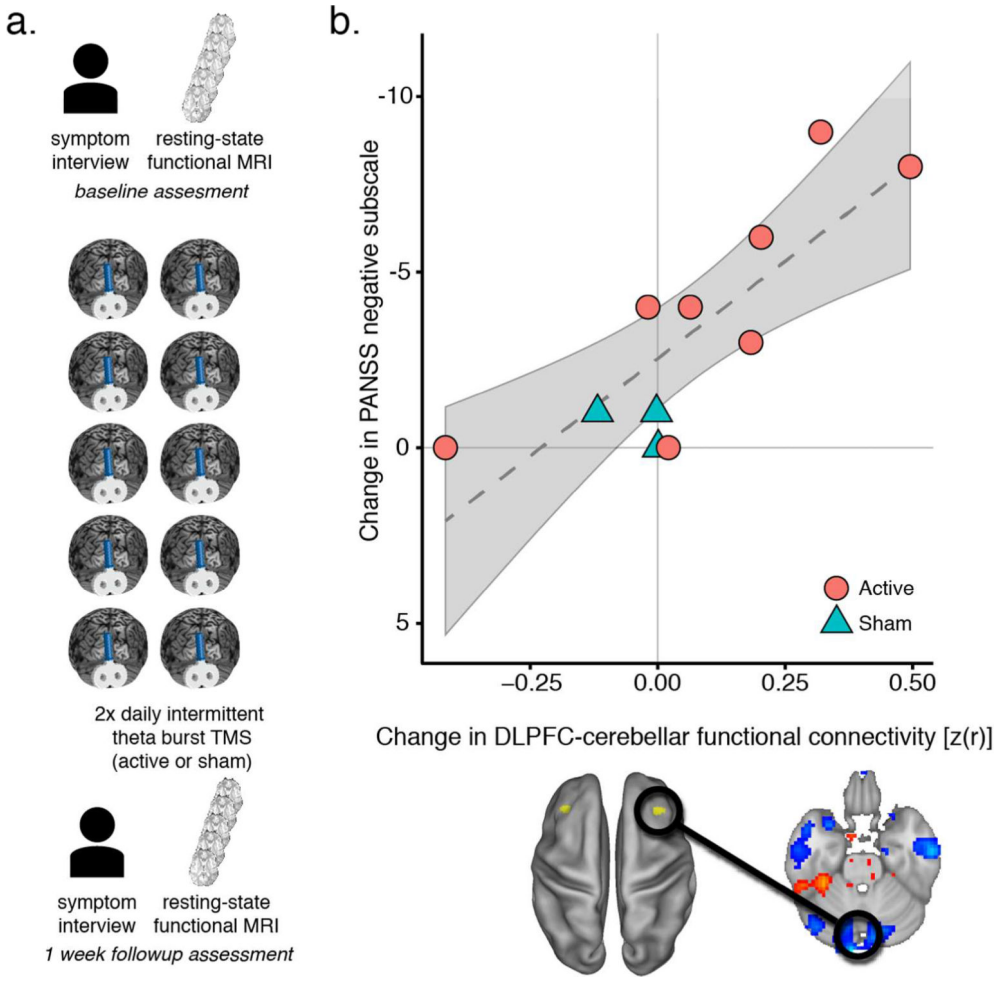

Figure 2.

One week of twice daily cerebellar intermittent theta burst modulates dorsolateral prefrontal cortex-cerebellar functional connectivity in schizophrenia patients. (a) TMS protocol overview: symptom scales and resting-state fMRI data at baseline and at 1 week followup after TMS. TMS was delivered to the midline cerebellum, two times a day separated by 4 hours, in a randomized trial with active and sham arms. (b) Change (followup-baseline) in PANSS negative symptoms is correlated with change (followup-baseline) in MDMR-identified right dorsolateral prefrontal cortex-cerebellar network functional connectivity.

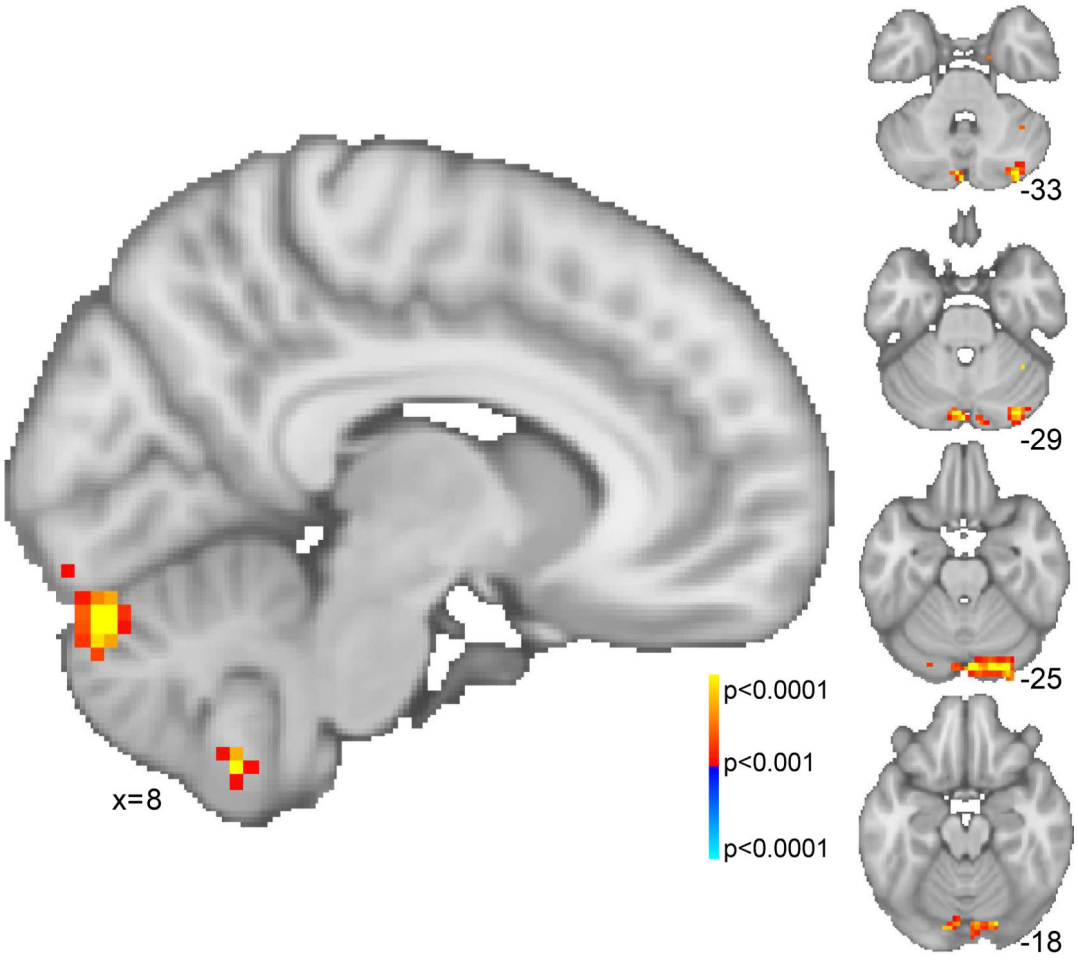

Figure 3.

Voxelwise analysis of change in functional connectivity from MDMR-identified right dorsolateral prefrontal cortex correlated with decrease in PANSS negative symptom score (red: increasing connectivity, blue: decreasing connectivity). Map is voxelwise thresholded at p<.001.

Table 1

Participant demographics

Network Identification Cohort		
Sex (n)		
Female	15	
Male	29	
Diagnosis (n)		
Schizoaffective	9	
Schizophrenia	35	
Age (mean, S.D.)	24.16	4.50
Race (n)		
African American	6	
Caucasian	27	
Asian	3	
Hispanic	1	
More than one	3	
Other	4	
BPRS (mean,S.D.)	41.75	9.47
MADRS (mean, S.D.)	10.93	9.61
SANS (mean, S.D.)	33.73	15.48
SAPS (mean, S.D.)	12.48	11.41
CPZE (mean, S.D.)	305.3	232.6
Network Validation Cohort		
Sex (n)		
Female	3	
Male	8	
Age (mean, S.D.)	35.55	10.50
Race (n)		
African American	2	
Caucasian	8	
Hispanic-Caucasian	1	
Calgary depression total (mean,S.D.)	5.18	4.92
PANSS positive subscale (mean, S.D.)	17.09	5.82
PANSS negative subscale (mean, S.D.)	23.00	10.65
PANSS general subscale (mean, S.D.)	35.82	11.70
CPZE (mean, S.D.)	614.2	606.5