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Clinical symptoms and alpha band resting-state functional connectivity imaging in patients with schizophrenia: implications for novel approaches to treatment

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Abstract

Background—Schizophrenia is associated with functional decoupling between cortical regions, but we do not know whether and where this occurs in low-frequency electromagnetic oscillations. The goal of this study was to use magnetoencephalography (MEG) to identify brain regions that exhibit abnormal resting-state connectivity in the alpha frequency range in patients with schizophrenia and investigate associations between functional connectivity and clinical symptoms in stable outpatient participants.

Method—Thirty patients with schizophrenia and fifteen healthy comparison participants were scanned in resting-state MEG (eyes closed). Functional connectivity MEG (fcMEG) data were reconstructed globally in the alpha range, quantified by the mean imaginary coherence between a voxel and the rest of the brain.

Results—In patients, decreased connectivity was observed in left pre-frontal cortex (PFC) and right superior temporal cortex while increased connectivity was observed in left extrastriate cortex and the right inferior PFC. Functional connectivity of left inferior parietal cortex was negatively related to positive symptoms. Low left PFC connectivity was associated with negative symptoms. Functional connectivity of midline PFC was negatively correlated with depressed symptoms. Functional connectivity of right PFC was associated with other (cognitive) symptoms.

Conclusions—This study demonstrates direct functional disconnection in schizophrenia between specific cortical fields within low-frequency resting-state oscillations. Impaired alpha coupling in frontal, parietal, and temporal regions is associated with clinical symptoms in these stable outpatients. Our findings indicate that this level of functional disconnection between cortical regions is an important treatment target in schizophrenia.

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Keywords

magnetoencephalography; functional connectivity; resting-state; schizophrenia; neuroimaging; symptoms

Introduction

There is a growing recognition in psychiatry research that it is critical to move beyond a receptor-based molecular neuropharmacology approach to psychiatric illness, and to engage in neural systems-based paradigms for treatment development. A promising approach is to develop a deeper understanding of networks of oscillatory patterns that emerge from specific neural circuits in mental illness, their function and dysfunction, and their response to interventions (*From Discovery to Cure*, NIMH, August 2010). Indeed, emerging research indicates that neural rhythms are impoverished in schizophrenia, for example, and that they play a key role not only in symptoms but also in deficits of cognition and sensory processing (1-3).

In recent years, evidence has begun to accumulate that a core feature of schizophrenia may be “disconnectivity” between cortical regions—a provocative and ambiguous term. *Functional* disconnectivity is often referred to as reduced statistical dependence between neurophysiological time series of separate brain regions. Recent studies that have examined such neural interactions using fMRI have provided evidence for “disconnection” in schizophrenia, with aberrant, diminished neural interactions (primarily between temporal and pre-frontal cortical fields) observed across a range of cognitive and affective tasks (4-10). The disconnectivity hypothesis has also been tested by examining cortical oscillations in high temporal fidelity electroencephalogram (EEG) recordings, and by estimating correlations, coherence and phase synchronization in oscillatory activity between electrode sites during cognitively demanding tasks (11-13). However, due to the spatial restrictions of EEG (e.g. artifacts due to volume conduction, reference electrode placement), it is unclear which specific brain regions and cortical fields contribute to changes in electrode coherence recorded in these patients during behavior.

Functional neuroimaging studies during behavior can also be confounded by a number of methodological factors, including subject compliance during performance of the task; the exclusion of participants who are unable to perform a demanding behavior; and the averaging across multiple trials to produce an adequate signal for analyses (14). Furthermore, differences in experimental design across studies (task, scan parameters) can make it difficult to generalize behaviorally-based findings in order to establish fundamental properties of atypical neural system function specific to patients with schizophrenia. Instead, an emerging focus in the imaging literature has been on “resting-state” experimental designs, which are not dependent on subject compliance or on task-specific factors (14-16). Both resting-state fMRI studies (17-23) and spontaneous EEG recordings (24-27) have identified changes in functional connectivity in patients with schizophrenia. These studies support the hypothesis that alterations in interactions between cortical regions are persistent even in the absence of behavior.

It is clear that a core functional feature of neural ensembles is their oscillatory activity at various frequencies, and the manner in which this represents the coordination, integration, and transmission of important computations both within and across neural systems (28). This understanding of a fundamental neural network property indicates that the study of “functional disconnectivity” in schizophrenia should also focus on delineating the details of how neuronal oscillations diverge and relate to clinical manifestations in this illness (1,3,29).

The present study had two goals. First, we aimed to evaluate the changes in spontaneous cortical connectivity at rest within the alpha frequency range (8-12Hz) in clinically stable participants with schizophrenia using functional connectivity magnetoencephalographic imaging (fcMEGI). fcMEGI refers to functional connectivity analysis (fc) of source-space reconstructions of MEG sensor data (MEGI). Alpha band oscillations represent a stable idling rhythm in the alert brain (30) and are coherent at large distances (>10cm; 30,31) making them an ideal candidate for functional interactions between distant cortical fields. Changes in alpha oscillatory dynamics have also been discussed as a feature of the cortex in schizophrenia (32,33). We predicted that specific cortical fields in the frontal and temporal lobes would exhibit reduced levels of resting-state functional connectivity in the schizophrenia group, consistent with previous reports in the literature. Second, in order to investigate whether abnormal alpha oscillations in specific cortical sectors are functionally related to clinical presentation, we examined associations between these measures of electromagnetic resting-state functional connectivity and symptom severity. Our goal here was to examine whether impaired alpha-band interactions between brain regions are related to psychopathology in schizophrenia, suggesting novel neural systems-based treatment approaches. We focus specifically on alpha as it is both the dominant oscillation in spontaneous electro- and magnetoencephalogram recordings in ~95% of individuals (34), and overlaps with resting-state networks identified in functional MRI (35,36). Our objective was to isolate the cortical fields that are normally coupled in the alpha range but that are disconnected in patients with schizophrenia, and to examine how decoupling may relate to clinical symptoms.

Methods and Materials

Participants

Thirty clinically stable, persistently ill, volunteer schizophrenia (SZ) participants were recruited from community mental health centers (mean age=38.4 SD=11.1, 7 women). Fifteen healthy comparison (HC) participants matched to the schizophrenia group on age, gender, and education, were recruited from the community via advertisement (mean age=43 SD=12.2, 4 women). Inclusion criteria were: Axis I diagnosis of schizophrenia (Structured Clinical Interview for DSM-IV, SCID, 37) or, for healthy subjects, no Axis I or Axis II psychiatric disorder (SCID-NP, 37); for all subjects, no current/previous substance dependence; good general physical health; age 18-60 years; English as first language; outpatient status (at least 3 months); no significant medication changes (dosage change >10%) during the study. Secondary (comorbid) diagnoses were present in 4 SZ participants (3 with major depressive disorder, 1 dysthymia).

All participants underwent MEG as a neurophysiological assessment at baseline prior to entering a randomized controlled trial of neuroplasticity-based cognitive training in schizophrenia (ClinicalTrials.gov NCT00312962). The MEG scan session which included a battery of auditory tasks (38) followed by a resting-state MEG scan. All procedures were approved by the UCSF Committee on Human Research, and all experiments were conducted in accordance with the Declaration of Helsinki.

Diagnostic and Symptom Assessments

All SZ participants met standard diagnostic criteria for schizophrenia (SCID, 37) and received the following clinical symptom ratings using an extended version of the Positive and Negative Syndrome Scale (PANSS-E, 39): Positive, Negative, Disorganized, Depressed, Anxious, and Other symptoms. The PANSS-E consists of the 30-item PANSS (40) supplemented with 10 items from the Comprehensive Assessment of Symptoms and History (CASH; 41). Ratings were made along a 7-point scale (1= absent, 3= mild, 7= extreme; 43)

and represent the consensus of two independent raters performed within two weeks of MEG scanning. In the SZ group, the mean rating on the positive subscale was 2.9 (SD=1.14), negative subscale was 2.8 (SD=0.79), depressed subscale was 3.2 (SD=1.11), disorganized subscale was 2.4 (SD=0.681), anxiety subscale was 1.8 (SD=0.647), and other symptoms was 2.5 (SD=0.78).

MRI Acquisition

Structural (T1-weighted) anatomical images were acquired for source space reconstruction, data visualization and second-level group analyses. Scanning was performed using a 3.0T GE Trio scanner. For each subject, a 3DSPRAGE high-resolution MRI was acquired (160 1mm slices; FOV = 260 mm, matrix = 256×256 , TE = 6 ms, TR = 35 ms, flip angle = 30°).

Magnetoencephalogram Recording

Four minutes of continuous recording (awake, supine position, eyes closed) were collected from all subjects using a 275-channel whole-head MEG system (MISL, Coquitlam, BC) consisting of 275 axial gradiometers (sampling rate= 600Hz). Three fiducial coils (nasion, left/right preauricular points) were placed to localize the position of the head relative to the sensor array. These points were later co-registered to a T1-weighted MRI in order to generate the head shape. Any participant with excessive within-run head movement based on fiducial coil position (>1cm) or who reported sleeping or feeling sleepy during this scan (<10% of all participants) was re-run.

Data Analysis

Source-space MEG-I reconstructions and functional connectivity metrics were computed using the Nutmeg software suite (<http://nutmeg.berkeley.edu>; 42). MEG-I can improve both the spatial resolution and signal detection abilities of MEG and overcome limitations inherent to this methodology (e.g. low SNR, radial versus tangential dipole moments; 43) enabling precise reconstructions of oscillatory activity in specific brain regions from MEG data (42,44,45). From the four minute dataset, a 60s, artifact-free segment of the data were selected for analysis (46). Artifact detection was performed qualitatively through a visual inspection of the sensor data after being anonymized and broken into four 60s trials, and only trials without excessive scatter (signal amplitude > 10 pT) due to eyeblink, saccades, head movement or EMG noise were selected for MEG-I analysis. MEG sensor data were filtered using a phase-preserving bandpass filter (fourth-order Butterworth; 1-20Hz bandpass) and reconstructed in source space using a minimum-variance adaptive spatial filtering technique (42,47). This approach provides an amplitude estimate at each element (voxel) derived through a linear combination of a spatial weighting matrix with the sensor data matrix. Tomographic reconstructions of the data were created by generating a multisphere head model based on a head shape obtained from each individual subject's structural MRI. A volume of interest (whole brain VOI) for lead field computation (grid size=2cm; approx. 300 voxels/participant) was automatically generated through a back-transformation of all the points within a spatially normalized MRI that corresponded to locations within the brain and excluding non-cerebral points. Therefore, the timecourse of activity at each voxel used for functional connectivity was computed for every location within the VOI, where each voxel within the VOI itself is an estimate of activity derived from inputs from all sensor recordings

For each subject, alpha frequency bins were selected around a peak power density centered on ~10Hz during the 60s epoch, selected from a broad 1-20Hz band with a frequency resolution of 1.17Hz (512 bins, as in 46). While peaks in the power spectra corresponding to oscillations in other frequency ranges (e.g. theta, low beta) were occasionally identified from subject to subject, only alpha peaks (power density peak between 8-12Hz) were identified

from this sampling window in all participants. Functional connectivity estimates were calculated using imaginary coherence (IC), a technique known to reduce overestimation biases in EEG/MEG data generated from common references, cross-talk and volume conduction (46,48). IC is able to sample interactions between source timeseries independent of the class of spatial filter used (46,49). Bivariate imaginary coherence values between two voxels (I_{xy}) within frequency window f were computed using the following:

$$I_{xy}(f) = \left| \frac{\sum_{k=1}^K X_k(f) Y_k^*(f)}{\sqrt{\sum_{k=1}^K |X_k(f)|^2 \sum_{k=1}^K |Y_k(f)|^2}} \right|$$

Global connectivity (GC) at each voxel was estimated by averaging across a single voxel's Fisher's Z-transformed IC values between that voxel and all other voxels in the grid the remaining elements in the reconstruction (46,48).

In a separate cohort of 20 healthy control participants, test-retest reliability of GC maps was evaluated by calculating a fixed-effects average intra-class correlation coefficient (ICC; 50). Good test-retest reliability was verified in the GC maps for both within session (ICC=0.61) and between the baseline scan and a 2-8 week follow-up session (ICC=0.64).

Group Statistics

T1-weighted MRIs were spatially normalized (5mm; SPM2 www.fil.ion.co.uk/spm2) and the transformation matrix from the normalization was then applied to each individual subject's GC map (GCM). Around 8500 voxels meeting cross-subject alignment were entered into the group analysis. Group contrasts (SZ vs. HC) were conducted using a non-parametric unpaired t-test (SnPM; 51). Average and variance maps were smoothed using a Gaussian kernel (20mm FWHM). Symptom rating scores from the PANSS were correlated with GC values at each voxel (Pearson's r). All tests were corrected for multiple comparisons using a False Discovery Rate (FDR) modified for dependency (52). We report peak activity at 5% FDR correction whenever possible, although to identify some main effects we used a less stringent 10% FDR threshold (53-55).

Results

Prior to functional connectivity analysis, a broad alpha band range was selected within a 6-14Hz window around the peak frequency (8-12Hz) for each participant. No peak in the power spectrum was consistently identified for bands greater than 12Hz. No significant differences in alpha power were identified between the HC and SZ groups ($p=0.36$). Although the frequency peak within alpha is known to be lower in schizophrenia (32,33) no significant differences in alpha window size were identified between the two groups for either the highpass (HC=6.60Hz (SD=0.41), SZ=6.68Hz (SD=0.65); $p=0.67$) or lowpass (HC=13.01 (SD=0.59), SZ=13.16 (SD=0.92); $p=0.55$) alpha cut-offs. Neuroleptic treatments are not known to affect alpha peaks specifically (56). A voxelwise correlation between medication dosage (chlorpromazine equivalents) and resting-state functional connectivity measures (global IC) yielded no significant results (average Spearman's $\rho=0.058$).

Global Connectivity Maps

The measures derived from imaginary coherence give us an estimate of global functional connectivity at each voxel, or the mean connectivity at each voxel between that region and

the rest of the brain (46). In the alpha range, robust global connectivity across functionally critical brain regions was present in both groups (Figure 1a). The areas that show the maximal global connectivity include regions of parietal, temporal and occipital cortices, including occipital and parietal regions along the midline such as the cuneus and pre-cuneus (Figure 1a).

A direct comparison between the global connectivity maps in the SZ and HC groups (Figure 1b) reveals regions that show relative changes in connectivity patterns in patients with schizophrenia.

Increases in functional connectivity in the SZ group were restricted to a region of the occipital lobe, as well as right pre-frontal cortex (Figure 1b, in red). Greater global connectivity scores in the SZ patients ($p < 0.05$, 10% FDR correction) were observed near the medial occipital gyrus (MOG; Figure 1b) in the left hemisphere in Brodmann's Area (BA) 19 (Table 1). SZ subjects also showed an overall *increase* in connectivity in the right inferior frontal gyrus (IFG; Figure 1b), near BA45 (Table 1; $p < 0.05$; 10% FDR).

Decreases in functional connectivity in the SZ group were found in multiple areas of the frontal and temporal lobes (Figure 1b, in blue). In the left hemisphere, decreased global connectivity values in SZ subjects were seen in BA6 and BA9 in left middle frontal gyrus (MFG; $p < 0.05$, 10% FDR), and a region of left precentral gyrus extending ventrally to the upper bank of the sylvian fissure (Pre-CG; $p < 0.05$, 10% FDR). In the right hemisphere, decreased connectivity ($p < 0.05$, 10% FDR) was found over the superior temporal gyrus (STG; Table 1).

Correlation: Global Connectivity Measures and Clinical Symptom Severity

For ratings of positive symptoms, the SZ participants recruited for this study fell within the range of absent to moderate-severe (1-5.5) on the PANSS-E. A significant negative correlation was found between positive symptom ratings and global connectivity scores in the left inferior parietal lobe ($r = -0.5511$, $p < 0.01$ 5% FDR; Figure 2a). This region, in BA40 (Table 1), overlaps areas known to be involved in speech comprehension and production (57). A similar association between low global connectivity and high positive symptom ratings was identified in a region within the right anterior insula (BA13; overlapping areas of reduced connectivity in the group analysis) although this correlation was weak ($r = -0.4792$, $p < 0.05$ uncorrected; Figure 2b).

For ratings of negative symptoms, SZ participants fell within the range of absent to moderate (1-4) (Figure 3). A significant relationship was found between negative symptom ratings and decreased connectivity in the left pre-frontal cortex in BA9/ BA10 of the middle frontal gyrus (Table 1, Figure 3; $r = -0.5164$, $p < 0.01$; 5% FDR). This region of BA9 overlaps with regions of left dorsolateral pre-frontal cortex (DLPFC) with reduced functional connectivity seen in the group comparison at relaxed statistical threshold ($p < 0.05$, uncorrected).

For ratings of depression, participants with schizophrenia fell within the range of absent to moderate-severe (1-5.5). SZ subjects with high ratings of depression had lower global connectivity over medial pre-frontal cortex (Figure 4a; $r = -0.5432$, $p < 0.01$; 5% FDR) centered on anterior cingulate cortex (ACC), an area known to play a strong role in cognitive control, self-evaluation and mood (58,59). Finally, we found a significant association in the "other" category of the PANSS-E (inattention, poor abstraction, etc.) and decreased functional connectivity in the right middle frontal gyrus (Figure 4b), over BA8 ($r = -0.5432$, $p < 0.01$; 5% FDR). Symptom ratings fell within the range of absent to moderate (1-4) in this "other" category. No significant relationship was observed between global

connectivity scores and disorganized symptoms or excited symptoms (10% FDR correction; Table 2).

Discussion

We present here, for the first time, direct evidence for functional disconnection between specific cortical regions in schizophrenia as demonstrated through disrupted spontaneous alpha oscillations--electromagnetic fluctuations that represent long-range communication between groups of neurons. Patterns of reduced alpha-band functional connectivity were correlated with symptoms of psychosis, depressed mood, and impaired cognition in these individuals. Our findings suggest that disconnectivity in the alpha range between key cortical regions reflects a core neurophysiologic correlate of clinical symptoms in schizophrenia, and thus may be a useful treatment target through pharmacological or behavioral interventions (3).

Functional Connectivity: Differences between patients and healthy comparison subjects

In the group comparison, connectivity of a large region of left DLPFC and pre-central gyrus was globally reduced in the SZ group (Figure 1b). This observation is congruent with previous reports of functional connectivity deficits of this region in schizophrenia using fMRI (18,60) as well as reductions in coherence in left hemisphere electrodes in EEG (26,61). Impaired function within DLPFC is thought to affect cognitive control, which in turn appears to be associated with many of the behavioral manifestations of schizophrenia (8).

As in left DLPFC, reductions in fMRI functional connectivity (10) and EEG alpha coherence (61) of the right temporal lobe have also been reported in individuals with schizophrenia both at rest and during behavior. Abnormal connectivity of the right MTG is believed to be related to impairments in auditory processing and attention (10), while abnormal activity within the right temporal lobe is often associated with auditory hallucinations (62-64).

Higher mean global IC values were identified in the patient group over the right inferior frontal gyrus (IFG) and the left medial occipital gyrus (MOG; Figure 1b). Increases in BOLD signal during a continuous performance task over the right IFG have been reported in patients with schizophrenia (65) as have been increased correlations between occipital EEG electrodes even in the absence of visual stimulation (66). Although a handful of neuroimaging studies have attributed increased neural activity in schizophrenia to an inefficiency in cortical processing (67) or heightened internal conflict and distractibility (18,21), these hypotheses have yet to be directly tested.

Functional Connectivity and Symptom Severity in Schizophrenia Subjects

Positive symptoms were negatively correlated with global IC values of the left inferior parietal lobe (IPL; Figure 2), a region which intersects the superior parietal-temporal lobe border (area sPT) near the sylvian fissure. Area sPT is a major component of a language network (57) and fMRI functional connectivity of this region during behavior correlates with the severity of auditory hallucinations (68). Abnormal auditory perceptual experiences may occur as a result of diminished functional connectivity of this area.

A strong relationship was seen in our subjects between reduced left BA9/10 connectivity and negative symptoms (Figure 3). This region, in left DLPFC, plays a strong role in the control of executive faculties, intention and motivation (69-71). Functional imaging studies have correlated low neural activity in this region to negative symptoms in patients with

schizophrenia (72). It is thus plausible that compromised functional integrity of this region could contribute to behavioral, emotional, and social withdrawal in this patient population.

In anterior cingulate cortex (ACC), reduced functional connectivity was significantly correlated with symptoms of depression and anxiety (Figure 4a). Patients with major depressive disorder have significantly reduced connectivity between ACC and limbic structures (amygdala, dorsomedial thalamus) in both active-state (73,74) and resting-state (75) fMRI studies. Our findings indicate that a common neurophysiological mechanism contributes to depressive symptoms in both schizophrenia and major depression.

The “other” symptoms category rates a range of symptoms, including cognitive features (in attention, disorientation; 40). In the SZ group, functional connectivity of right DLPFC (including BA8) was negatively correlated with these ratings (Figure 4b). Right-lateralized DLPFC function is thought to play a role in memory retrieval (76,77) and cognitive control (78,79). Estimates of right DLPFC functional connectivity derived from fMRI studies show reduced interactions between this region in patients with schizophrenia across a wide range of cognitive tasks (80-81). Our data suggest that a relationship between right DLPFC functional connectivity and cognition may also be present in the brain’s resting-state, indicating a potential treatment target (82).

Functional Significance of Atypical Alpha Connectivity in Schizophrenia

Alpha oscillations are a stable rhythm thought to be generated through reciprocal excitatory and inhibitory neuronal interactions (30,83). Coherent activity between cortical sources cannot be explained by thalamic inputs alone (84-86), suggesting that these oscillations are a reliable marker of long-range cortico-cortical interactions in the brain (87,88). Our data is consistent with previous EEG studies outlining the topology and magnitude of compromised oscillatory activity and non-linear alpha interdependence in schizophrenia (89-91). While deviations in oscillatory power across many frequency bands (including alpha) have been identified using MEG (92-94), this is the first investigation to use MEG source data (MEGI) to examine spontaneous alpha functional connectivity directly in schizophrenia. Disruptions in alpha coherence represent a lack of synchrony *between* brain regions, which itself may be due to either a reduction in local computational processing and/or reduced neural synchrony across cortical fields.

Relationship between MEG and fMRI resting-state connectivity

In schizophrenia, where the prevailing model of the disease is built upon an *a priori* assumption of dysfunctional connectivity (95,96), it is difficult to make a distinction between deficits in functional connectivity and abnormal levels of activity *within* a cortical field. Due to temporal limitations of fMRI, functional connectivity metrics of cerebral blood flow are restricted to models of functionally significant networks at extremely low frequency ranges ($<0.1\text{Hz}$; 97). Active-state fMRI studies can be contaminated by non-neural, physiological interactions unrelated to brain activity (98,99). Resting-state imaging paradigms provide a unique advantage to resolving this conflict between abnormal activity and connectivity. It is not clear how reductions in fMRI connectivity relate to lowered MEG connectivity in 8-12Hz oscillations. Simultaneous EEG/fMRI studies have shown that reduced alpha power correlates with increased BOLD signal change in posterior brain regions (100,101). Interestingly, although these functional connectivity metrics in schizophrenia are derived from very divergent imaging modalities, they highlight a common theme of lack of coordination or integration of normal patterns of cortical information processing.

Limitations of study

It is important to note that in any psychiatric disorder there is a considerable degree of heterogeneity within the population that is being studied. Our sample included subjects ranging from recent onset to those who had been ill for decades. Clinical heterogeneity in our sample may also play a role in any observed associations—or lack of associations—between coherence and symptom ratings. Further, in these kinds of studies, it is difficult to dissect out neurophysiologic findings which represent the schizophrenia “endophenotype” from those which represent the cumulative effects of illness burden or which represent the current clinical state. Future work will need to examine if the reductions in functional connectivity that we report here are altered over the course of successful treatment.

Changes in fcMEGI we observe in the schizophrenia group could be arguably interpreted as an “inability to rest” for patients in general (102), potentially impacting all studies of activity and connectivity in schizophrenia using task-evoked designs (103). However, we observe no differences in alpha power or distribution of alpha peak which would indicate heightened alpha activity. Furthermore, a strong relationship between regional connectivity and clinical symptoms that we observe suggest that if there is an “inability to rest”, it is manifested in patterns of functional interactions and is of pathological importance.

As a clinically stable cohort, all of the participants were medicated, making it difficult to discern how their psychiatric medications impact MEG alpha coherence at rest. We found no significant correlation between level of medication and functional connectivity. Therefore, it is reasonable to assume that the reductions in alpha-band connectivity we identify here were only marginally affected by medication and that these effects would also be observed in an unmedicated patient sample.

Conclusions

The current study provides novel and compelling evidence for how disrupted long-range neural functional connectivity (as evidenced through deviations in coherence of resting-state alpha) contributes to characteristic clinical manifestations in schizophrenia. Although this relationship is complex, an understanding of the oscillatory mechanisms through which networked brain regions normally cooperate and how these networks relate to disruptions in cognition and affect in psychiatric illnesses could lead to innovations in treatment conceptualization and development.

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Figure 1.

Global connectivity maps (GCMs) and data from a group comparison (non-parametric unpaired t-test) between patient and control GCMs. (A) In both the SZ and HC group, strong alpha imaginary coherence is seen in the GCMs in the posterior regions of the brain. (B) In patients with schizophrenia, greater connectivity (in red) is present in a region of the right inferior frontal gyrus (IFG) and left medial occipital gyrus (MOG). In addition, multiple cortical fields in the patient group had lower levels of functional connectivity (in blue). Connectivity of regions in the left frontal lobe, including cortex along the middle frontal gyrus (MFG) and pre-central gyrus (PreCG) were reduced in patients with schizophrenia. In the right hemisphere, connectivity of the superior temporal gyrus (STG) was significantly reduced in the patient group. Areas with greater connectivity in the control group are abbreviated in pink, areas with greater connectivity in the patient group are abbreviated in green. Statistical maps are thresholded and superimposed over a rendering of the MNI template brain through MRICro (<http://www.sph.sc.edu/comd/rorden/mricro.html>).

Figure 2.

Results from a pairwise correlation between global connectivity (GC) measures in the patient group with positive symptom ratings from the Positive and Negative Symptom Scale, Extended (PANSS-E). Voxels that are negatively correlated with symptom strength are circled in blue and color scaled blue to red. Connectivity of a region in the right hemisphere in Brodmann's Area 13 (BA13) was negatively correlated with positive symptoms assessed in these patients. We also identified a negative relationship between GC measures and positive symptoms in a region of the left inferior parietal lobe, in Brodmann's Area 40 (BA40). Statistical maps (Pearson's r) are thresholded ($p < 0.05$, uncorrected) and superimposed over a rendering of the MNI template brain through MRICro.

Figure 3.

Results from a pairwise correlation between global connectivity (GC) measures in the patient group with negative symptom ratings from the PANSS-E. One region of left PFC, in Brodmann's Area 10 (BA10) was significantly correlated with negative symptoms in these patients. Left BA10 in this analysis overlapped a region in aPFC with lower functional connectivity in the patient group. The direction of this trend suggests that low global connectivity in BA10 is related to high negative symptom ratings on the PANSS-E in this group. Conventions as in previous figures.

Figure 4.

Results from a pairwise correlation between global connectivity (GC) measures in the patient group with extended scores from the PANSS-E. A) Relationship between alpha-band functional connectivity and level of depression (as assessed by the PANSS-E) in patients with schizophrenia. Low IC values in a large region of cortex along the medial wall (in the anterior cingulate) were associated with high ratings for depression in patients with schizophrenia. B) Relationship between GC measures and assessment ratings of “other” impairments as assessed by the PANSS-E, including cognitive deficits. In the right hemisphere, a negative relationship was identified between global connectivity of the right MFG, in Brodmann’s Area 8 (BA8) and these symptoms in patients with schizophrenia. Conventions as previous figures.

Table 1

Region	Abbrev	Hemi	BA	x	y	z	p	T
<i>Group Comparison</i>								
Pre-Central Gyrus	Pre-CG	L	6	-55	5	10	0.008	2.57
Middle Frontal Gyrus	MFG	L	6/9	-40	10	40	0.009	2.16
<i>Superior Temporal</i>								
Gyrus	STG	R	22	60	5	0	0.004	2.69
Inferior Frontal Gyrus	IFG	R	45	55	40	0	0.007	2.99
Middle Occipital Gyrus	MOG	L	19	-40	-90	10	0.007	2.55
<i>Positive Symptoms</i>								
Inferior Parietal Lobe	IPL	L	40	-60	-35	25	0.002	-0.55
<i>Negative Symptoms</i>								
Middle Frontal Gyrus	MFG	L	9/10	-40	50	25	0.004	-0.51
<i>Depressed Symptoms</i>								
Anterior Cingulate								
Cortex	ACC	L/R	32	5	30	30	0.002	-0.54
<i>Other Symptoms</i>								
Middle Frontal Gyrus	MFG	R	8	40	25	50	0.002	-0.54

Table 2

Region	Abbrev	Hemi	BA	x	y	z	r	p
<i>Disorganized Symptoms</i>								
Superior Temporal Gyrus	STG	L	22	-40	-55	10	0.455	0.012
Inferior Frontal Gyrus	IFG	R	44	60	15	15	-0.387	0.035
<i>Excited Symptoms</i>								
Cuneus	CU	L	7	-20	-60	55	0.385	0.036
Middle Temporal Gyrus	MTG	L	39	-50	-75	5	0.442	0.015