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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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Background: Schizophrenia (SZ) 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.

Methods: Thirty patients with SZ and 15 healthy comparison participants were scanned in resting-state MEG (eyes closed). Functional connectivity MEG source 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 prefrontal cortex (PFC) and right superior temporal cortex, whereas 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 SZ 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 SZ.

Key Words: Functional connectivity, magnetoencephalography, neuroimaging, resting-state, schizophrenia, symptoms

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*, National Institute of Mental Health, August 2010). Indeed, emerging research indicates that neural rhythms are impoverished in schizophrenia (SZ), 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 SZ might 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 with

functional magnetic resonance imaging (fMRI) have provided evidence for “disconnection” in SZ, with aberrant, diminished neural interactions (primarily between temporal and prefrontal 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 to establish fundamental properties of atypical neural system function specific to patients with SZ. 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 SZ. These studies support the hypothesis that alterations in interactions between cortical regions are persistent even in the absence of behavior.

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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 SZ 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 (8–12 Hz) in clinically stable participants with SZ with functional connectivity magnetoencephalographic imaging (fcMEGI). The fcMEGI refers to functional connectivity analysis of source-space reconstructions of magnetoencephalographic (MEG) sensor data. Alpha band oscillations represent a stable idling rhythm in the alert brain (30) and are coherent at large distances (>10 cm) (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 SZ (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 SZ group, consistent with previous reports in the literature. Second, 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 SZ, suggesting novel neural systems-based treatment approaches. We focus specifically on alpha, because it is both the dominant oscillation in spontaneous EEG and MEG recordings in approximately 95% of individuals (34) and overlaps with resting-state networks identified in fMRI (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 SZ and to examine how decoupling might relate to clinical symptoms.

Methods and Materials

Participants

Thirty clinically stable, persistently ill, volunteer SZ participants were recruited from community mental health centers (mean age = 38.4 years, SD = 11.1 years, 7 women). Fifteen healthy comparison (HC) participants matched to the SZ group on age, gender, and education were recruited from the community via advertisement (mean age = 43 years, SD = 12.2 years, 4 women). Inclusion criteria were: Axis I diagnosis of SZ (Structured Clinical Interview for DSM-IV [SCID]) (37) or, for HCs, 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); and no significant medication changes (dosage change >10%) during the study. Secondary (comorbid) diagnoses were present in four SZ participants (three with major depressive disorder, one with dysthymia).

All participants underwent MEG as a neurophysiological assessment at baseline before entering a randomized controlled trial of neuroplasticity-based cognitive training in SZ (<http://clinicaltrials.gov>, NCT00312962). The MEG scan session included a battery of auditory tasks (38) followed by a resting-state MEG scan. All procedures were approved by the University of California at San Francisco

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 SZ (SCID) (37) and received the following clinical symptom ratings with 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 2 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 = .79), depressed subscale was 3.2 (SD = 1.11), disorganized subscale was 2.4 (SD = .681), anxiety subscale was 1.8 (SD = .647), and on other symptoms was 2.5 (SD = .78).

Magnetic Resonance Imaging Acquisition

Structural (T1-weighted) anatomical images were acquired for source space reconstruction, data visualization, and second-level group analyses. Scanning was performed with a 3.0T GE Trio scanner (GE Medical Systems, Waukesha, Wisconsin). For each subject, three-dimensional magnetization prepared rapid gradient echo (MPRAGE) high-resolution magnetic resonance imaging (MRI) was acquired (160 1-mm slices; field of view = 260 mm, matrix = 256 × 256, echo time = 6 msec, repetition time = 35 msec, flip angle = 30°).

MEG Recording

Four minutes of continuous recording (awake, supine position, eyes closed) were collected from all subjects with a 275-channel whole-head MEG system (MISL, Coquitlam, British Columbia, Canada) consisting of 275 axial gradiometers (sampling rate = 600 Hz). 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 to generate the head shape. Any participant with excessive within-run head movement based on fiducial coil position (>1 cm) 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 with the Nutmeg software suite (<http://nutmeg.berkeley.edu>) (42). The MEG-I can improve both the spatial resolution and signal detection abilities of MEG and overcome limitations inherent to this methodology (e.g., low signal/noise ratio, radial versus tangential dipole moments) (43), enabling precise reconstructions of oscillatory activity in specific brain regions from MEG data (42,44,45). From the 4-min dataset, a 60-sec, artifact-free segment of the data was selected for analysis (46). Artifact detection was performed qualitatively through a visual inspection of the sensor data after being anonymized and broken into four 60-sec trials, and only trials without excessive scatter (signal amplitude >10 pT) due to eyeblink, saccades, head movement, or electromyograph noise were selected for MEG source data analysis. The MEG sensor data were filtered with a phase-preserving bandpass filter (fourth-order Butterworth; 1–20 Hz bandpass) and reconstructed in source space with 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 multi-sphere head model based on a head shape obtained from the structural MRI of each individual subject. A volume of interest (whole brain VOI) for lead field computation (grid size = 2 cm; approximately 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 excluded noncerebral 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 approximately 10 Hz during the 60-sec epoch, selected from a broad 1–20 Hz band with a frequency resolution of 1.17 Hz (512 bins, as in Guggisberg *et al.* [46]). Although 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 and 12 Hz) were identified from this sampling window in all participants. Functional connectivity estimates were calculated with 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). Imaginary coherence is able to sample interactions between source timeseries, independent of the class of spatial filter used (46,49). Bivariate IC values between two voxels (I_{xy}) within frequency window f were computed with the following:

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

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 HC participants, test-retest reliability of global connectivity maps (GCMs) was evaluated by calculating a fixed-effects average intra-class correlation coefficient (ICC) (50). Good test-retest reliability was verified in the GCMs for both within-session (ICC = .61) and between-the-baseline scans and a 2–8-week follow-up session (ICC = .64).

Group Statistics

The T1-weighted MRIs were spatially normalized (5 mm; SPM2 <http://www.fil.ion.ucl.ac.uk/spm/>), and the transformation matrix from the normalization was then applied to the GCM of each individual subject. Approximately 8500 voxels meeting cross-subject alignment were entered into the group analysis. Group contrasts (SZ vs. HC) were conducted with a nonparametric unpaired t test (51). Average and variance maps were smoothed with a Gaussian kernel (20 mm full-width-at-half-maximal). Symptom rating scores from the PANSS were correlated with GC values at each voxel (Pearson's r). All tests were corrected for multiple comparisons with 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

Before functional connectivity analysis, a broad alpha band range was selected within a 6–14-Hz window around the peak

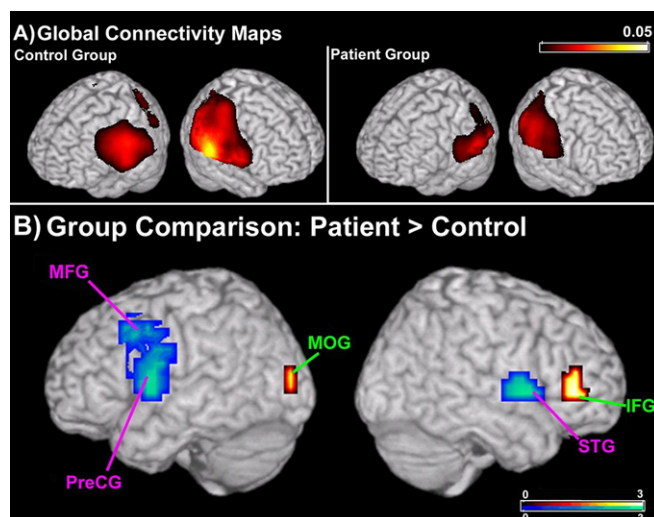


Figure 1. Global connectivity maps (GCMs) and data from a group comparison (nonparametric unpaired t test) between patient and control GCMs. **(A)** In both the schizophrenia and healthy control group, strong alpha imaginary coherence is seen in the GCMs in the posterior regions of the brain. **(B)** 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 precentral 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 Montreal Neurological Institute template brain through MRICro (<http://www.sph.sc.edu/comd/rorden/mricro.html>).

frequency (8–12 Hz) for each participant. No peak in the power spectrum was consistently identified for bands >12 Hz. No significant differences in alpha power were identified between the HC and SZ groups ($p = .36$). Although the frequency peak within alpha is known to be lower in SZ (32,33), no significant differences in alpha window size were identified between the two groups for either the highpass (HC = 6.60 Hz [SD = .41], SZ = 6.68 Hz [SD = .65]; $p = .67$) or lowpass (HC = 13.01 [SD = .59], SZ = 13.16 [SD = .92]; $p = .55$) 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 $\rho = .058$).

GCMs

The measures derived from IC 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 GC across functionally critical brain regions was present in both groups (Figure 1A). The areas that show the maximal GC include regions of parietal, temporal, and occipital cortices, including occipital and parietal regions along the midline such as the cuneus and precuneus (Figure 1A).

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

Increases in functional connectivity in the SZ group were restricted to a region of the occipital lobe as well as right PFC (Figure

Table 1. Group Differences in Global Connectivity and Correlations Between GC and Symptoms (FDR Corrected)

Region	Abbreviation	Hemisphere	BA	x	y	z	<i>p</i>	<i>T</i>
Group Comparison								
Precentral gyrus	Pre-CG	L	6	−55	5	10	.008	2.57
Middle frontal gyrus	MFG	L	6/9	−40	10	40	.009	2.16
Superior temporal gyrus	STG	R	22	60	5	0	.004	2.69
Inferior frontal gyrus	IFG	R	45	55	40	0	.007	2.99
Middle occipital gyrus	MOG	L	19	−40	−90	10	.007	2.55
Region	Abbreviation	Hemisphere	BA	x	y	z	<i>p</i>	<i>r</i>
Positive Symptoms								
Inferior parietal lobe	IPL	L	40	−60	−35	25	.002	−.55
Negative Symptoms								
Middle frontal gyrus	MFG	L	9/10	−40	50	25	.004	−.51
Depressed Symptoms								
Anterior cingulate cortex	ACC	L/R	32	5	30	30	.002	−.54
Other Symptoms								
Middle frontal gyrus	MFG	R	8	40	25	50	.002	−.54

BA, Brodmann area; L, left; R, right.

1B, in red). Greater GC scores in the SZ patients ($p < .05$, 10% FDR correction) were observed near the medial occipital gyrus (Figure 1B) in the left hemisphere in Brodmann area (BA) 19 (Table 1). The SZ subjects also showed an overall increase in connectivity in the right inferior frontal gyrus (IFG) (Figure 1B), near BA45 (Table 1) ($p < .05$; 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 GC values in SZ subjects were seen in BA6 and BA9 in left middle frontal gyrus ($p < .05$, 10% FDR) and a region of left precentral gyrus extending ventrally to the upper bank of the sylvian fissure (Pre-CG; $p < .05$, 10% FDR). In the right hemisphere, decreased connectivity ($p < .05$, 10% FDR) was found over the superior temporal gyrus (Table 1).

Correlation: GC 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 GC scores in the left inferior parietal lobe ($r = -.5511$, $p < .01$ 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 GC 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 ($r = -.4792$, $p < .05$ 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 PFC in BA9/BA10 of the middle frontal gyrus (Figure 3, Table 1) ($r = -.5164$, $p < .01$; 5% FDR). This region of BA9 overlaps with regions of left dorsolateral prefrontal cortex (DLPFC) with reduced functional connectivity seen in the group comparison at relaxed statistical threshold ($p < .05$, uncorrected).

For ratings of depression, participants with SZ fell within the range of absent to moderate-severe (1–5.5). The SZ subjects with high ratings of depression had lower GC over medial PFC (Figure 4A) ($r = -.5432$, $p < .01$; 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 (inatten-

tion, poor abstraction, etc.) and decreased functional connectivity in the right middle frontal gyrus (Figure 4B), over BA8 ($r = -.5432$, $p < .01$; 5% FDR). Symptom ratings fell within the range of absent to moderate (rating: 1–4) in this “other” category. No significant relationship was observed between GC scores and disorganized symptoms or excited symptoms (10% FDR correction) (Table 2).

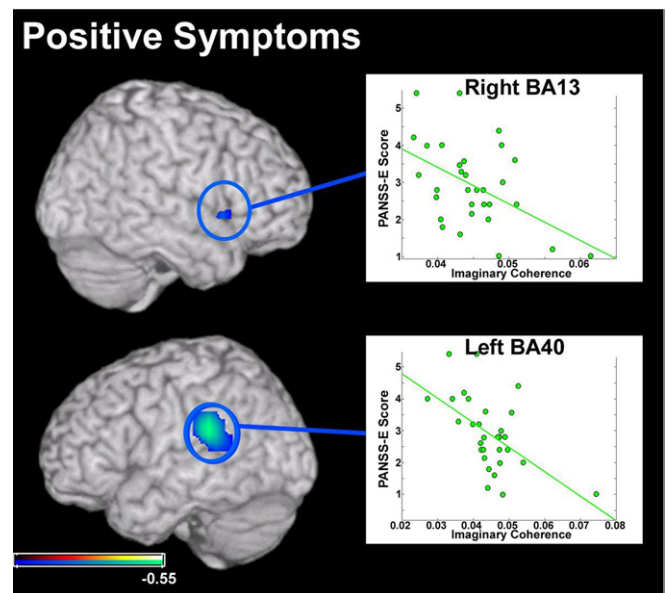


Figure 2. Results from a pairwise correlation between global connectivity measures in the patient group with positive symptom ratings from the Positive and Negative Symptom Scale, Extended (PANSS-E). Voxels that are negatively correlated with symptom strength are circled in blue and color-scaled blue to azure. Connectivity of a region in the right hemisphere in Brodmann area (BA) 13 was negatively correlated with positive symptoms assessed in these patients. We also identified a negative relationship between global connectivity measures and positive symptoms in a region of the left inferior parietal lobe, in BA40. Statistical maps (Pearson's r) are thresholded ($p < .05$, uncorrected) and superimposed over a rendering of the Montreal Neurological Institute template brain through MRICro.

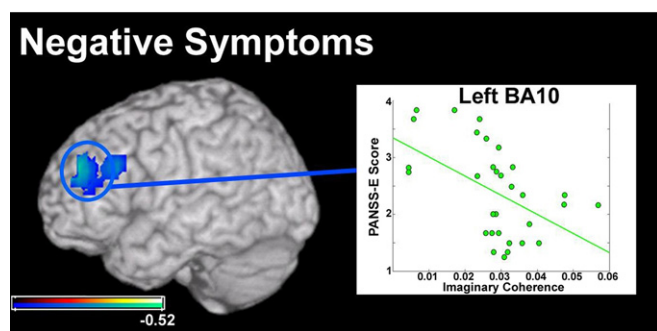


Figure 3. Results from a pairwise correlation between global connectivity (GC) measures in the patient group with negative symptom ratings from the PANSS-E. One region of left prefrontal cortex, in BA10 was significantly correlated with negative symptoms in these patients. Left BA10 in this analysis overlapped a region in anterior prefrontal cortex with lower functional connectivity in the patient group. The direction of this trend suggests that low GC in BA10 is related to high negative symptom ratings on the PANSS-E in this group. Abbreviations as in Figure 2.

Discussion

We present here, for the first time, direct evidence for functional disconnection between specific cortical regions in SZ, 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 disconnection in the alpha range between key cortical regions reflects a core neurophysiologic correlate of clinical symptoms in SZ and thus might be a useful treatment target through pharmacological or behavioral interventions (3).

Functional Connectivity: Differences Between Patients and HC Subjects

In the group comparison, connectivity of a large region of left DLPFC and precentral 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 SZ with 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 seems to be associated with many of the behavioral manifestations of SZ (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 SZ both at rest and during behavior. Abnormal connectivity of the right middle temporal gyrus is believed to be related to impairments in auditory processing and attention (10), whereas 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 IFG and the left medial occipital gyrus (Figure 1B). Increases in blood oxygen level dependent signal during a continuous performance task over the right IFG have been reported in patients with SZ (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 SZ 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 SZ Subjects

Positive symptoms were negatively correlated with global IC values of the left inferior parietal lobe (Figure 2), a region that 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 might 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 SZ (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 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 SZ and major depression.

The “other” symptoms category rates a range of symptoms, including cognitive features (in attention, disorientation) (40). In

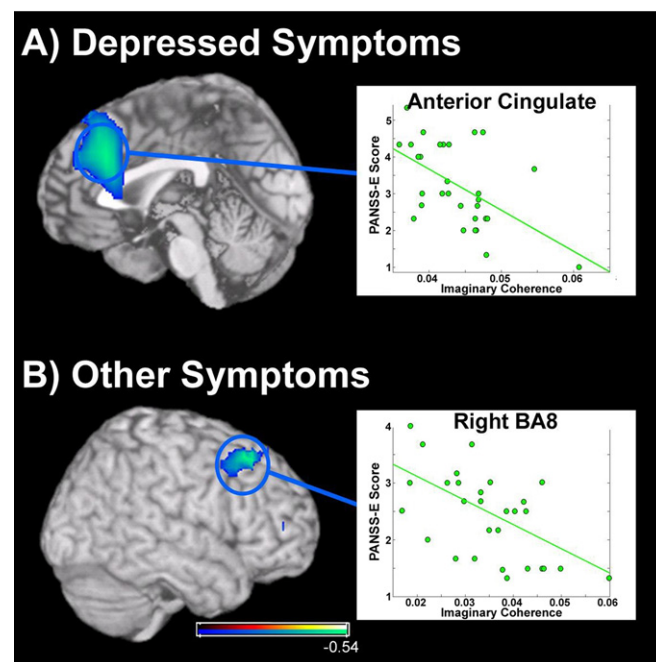


Figure 4. Results from a pairwise correlation between GC measures in the patient group with extended scores from the PANSS-E. (A) Relationship between alpha-band functional connectivity and level of depression (as assessed by the PANSS-E) in patients with schizophrenia. Low imaginary coherence values 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 GC of the right middle frontal gyrus in BA8 and these symptoms in patients with schizophrenia. Abbreviations as in Figures 2 and 3.

Table 2. Correlations Between Global Connectivity and Symptom Scores (Uncorrected)

Region	Abbreviation	Hemisphere	BA	x	y	z	r	p
Disorganized Symptoms								
Superior temporal gyrus	STG	L	22	−40	−55	10	.455	.012
Inferior frontal gyrus	IFG	R	44	60	15	15	−.387	.035
Excited Symptoms								
Cuneus	CU	L	7	−20	−60	55	.385	.036
Middle temporal gyrus	MTG	L	39	−50	−75	5	.442	.015

Abbreviations as in Table 1.

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 SZ across a wide range of cognitive tasks (80,81). Our data suggest that a relationship between right DLPFC functional connectivity and cognition might also be present in the resting-state of the brain, indicating a potential treatment target (82).

Functional Significance of Atypical Alpha Connectivity in SZ

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 are consistent with previous EEG studies outlining the topology and magnitude of compromised oscillatory activity and nonlinear alpha interdependence in SZ (89–91). Although deviations in oscillatory power across many frequency bands (including alpha) have been identified with MEG (92–94), this is the first investigation to use MEG source data to examine spontaneous alpha functional connectivity directly in SZ. Disruptions in alpha coherence represent a lack of synchrony between brain regions, which itself might 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 SZ, 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 (<.1 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 8–12-Hz oscillations. Simultaneous EEG/fMRI studies have shown that reduced alpha power correlates with increased blood oxygen level dependent signal change in posterior brain regions (100,101). Interestingly, although these functional connectivity metrics in SZ 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.

Study Limitations

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 might also play a role in any observed associations—or lack of associations—between coherence and symptom ratings. Furthermore, in these kinds of studies, it is difficult to dissect out neurophysiologic findings that represent the SZ “endophenotype” from those that represent the cumulative effects of illness burden or that represent the current clinical state. Future work will need to examine whether the reductions in functional connectivity that we report here are altered over the course of successful treatment.

Changes in fcMEG we observe in the SZ group could arguably be interpreted as an “inability to rest” for patients in general (102), potentially impacting all studies of activity and connectivity in SZ with task-evoked designs (103). However, we observe no differences in alpha power or distribution of alpha peak that 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 SZ. 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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[ClinicalTrials.gov](http://clinicaltrials.gov): Neuroscience-Guided Remediation of Cognitive Deficits in Schizophrenia; <http://clinicaltrials.gov/ct2/show/NCT00312962?term=NCT00312962&rank=1;NCT00312962>.

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