Increased Resting-State Gamma-Band Connectivity in First-Episode Schizophrenia

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Background: Schizophrenia has long been suggested to represent a disorder with prominent neural dysconnectivity. Gamma-band oscillations are highly relevant in this context, due both to their proposed involvement in neuronal synchronization and to their association with neurotransmitter systems relevant for schizophrenia. Several task-related studies have confirmed reduced power and synchronization of gamma-band oscillations in schizophrenia, but it has been suggested that these findings might not apply to the resting state. The present study aimed to investigate resting-state gamma-band connectivity in patients with schizophrenia.

Methods: Sixty-four channel resting-state electroencephalography (eyes closed) was recorded in 22 patients with first-episode schizophrenia and 22 healthy controls matched for age and gender. Orthogonalized power envelope correlation was used as a measure of connectivity across 80 cortical regions at 40 Hz. Mean connectivity at each region was compared across groups using the nonparametric randomization approach. Additionally, the network-based statistic was applied to identify affected networks in patients.

Results: Patients displayed increased mean functional gamma-band connectivity compared to controls in the left Rolandic operculum. Network-based analyses indicated increased connectivity in patients within a strongly lateralized network consisting mainly of left inferior frontal/orbitofrontal, lateral and medial temporal, and inferior parietal areas. Within this network, gamma-band connectivity was higher in patients with low positive and disorganization symptom levels.

Conclusions: The present study provides a link between resting-state gamma-band connectivity and the core symptoms of schizophrenia. The observed findings are different than those reported by task-related studies, suggesting that resting-state studies might reveal new aspects in the pathophysiology of schizophrenia.

Key words: psychosis/positive symptoms/disorganization/EEG/functional connectivity/power envelope correlation

Introduction

It has been long suggested that the complex clinical and cognitive symptoms of schizophrenia are best explained in terms of disturbed coordination of distributed brain networks rather than as hypofunctionality of specific brain regions.1,2 A large body of functional magnetic resonance imaging studies have identified connectivity disturbances in patients with schizophrenia.3 However, following the seminal proposition that communication within neuronal networks is mediated by synchronous neural oscillations,4,6 there has also been growing interest in the oscillatory mechanisms underlying these connectivity disturbances as revealed by electroencephalography (EEG) and magnetencephalography (MEG). Gamma-band oscillations occupy a central place within this framework because they are involved in both local and large-scale neuronal synchronization underlying a broad range of perceptual and higher-order cognitive functions,4,5,7 such as those typically impaired in schizophrenia. Moreover, recent evidence links gamma-band oscillations to neurotransmitter systems and gene variants associated with schizophrenia: The generation of gamma-band oscillations depends on a closed feedback loop involving parvalbumin-positive GABAergic interneurons and glutamatergic pyramidal cells.8,9 Several pharmacological and genetic disease models of schizophrenia interfere with the function of this microcircuit and lead to disruption of gamma-band oscillations, while a significant amount of evidence points to disturbances of elements of the gamma-generator loop in patients with schizophrenia.7,10
Several studies in patients with schizophrenia have consistently reported reduced local gamma-band oscillatory power during a variety of perceptual and cognitive tasks, as well as reduced locking of the gamma oscillation phase to stimulus presentation. More recent MEG studies have extended these findings to the high gamma range (>60 Hz), demonstrating deficits in patients compared to healthy controls during perceptual processing. Similar deficits have been described in unaffected first-degree relatives of patients with schizophrenia, suggesting that abnormalities of gamma-band oscillations might represent an intermediate phenotype for the illness. Emerging evidence also suggests that not only local gamma-band responses but also the long-range synchronization of gamma-band oscillations are reduced during stimulus processing in patients.

However, the pattern of gamma-band oscillation abnormalities in schizophrenia might be less straightforward than the above studies suggest. For one, gamma-band responses often correlate with positive psychotic symptoms in a counter-intuitive direction, with higher (i.e., more “normal”) gamma-band activity corresponding to increased symptom load. Second, pathological models of schizophrenia do not always predict reduced gamma-band activity: A recent computational model demonstrated that disruptions within the local gamma-generator circuit or reduced GABAAergic interneuron output (which is expected to be the case in schizophrenia) led indeed to deficits in gamma-band activity; however, the prominent glutamate hypothesis of schizophrenia postulates impaired N-methyl-D-aspartate (NMDA) glutamatergic receptor signaling, which resulted in increased gamma-band power in the modeled network, consistent with the effects of acute administration of NMDA receptor antagonists on humans and animals. Indeed, increased spontaneous gamma-band activity has often been reported in schizophrenia, although findings are discordant, with other studies showing no change or even reduced resting-state gamma-band power in patients.

However, power cannot necessarily be used to draw inferences with respect to synchronization because the 2 measures can dissociate from each other. As already discussed, gamma oscillations are postulated to play a major role in synchronization between cortical areas. This role is not limited to neural synchrony of local brain networks, but also extends to large-scale interactions. Therefore, investigations of connectivity, rather than power, in the resting state might contribute to disentangling the discrepancies of previous research, providing new insights into the role of gamma-band connectivity in the pathophysiology of the disorder. So far, only 2 studies have assessed gamma-band synchronization in patients with schizophrenia. Their results were inconsistent, with one study reporting reduced global, scalp-level gamma-band coordination in patients with schizophrenia over the right frontal area, while the other study did not find any significant differences in gamma-band coherence between patients and controls. However, the measures used to assess connectivity in the above studies did not address an important problem associated with EEG/MEG data, namely that measures of brain interaction may be distorted by signal mixing due to volume conduction and, for EEG, by the use of a common reference, which limits the interpretability of findings. Therefore, the aim of the present study was to investigate EEG resting-state connectivity in the gamma frequency range in patients with schizophrenia compared to healthy controls, using source-level analysis and an appropriate interaction measure that is robust against spurious interaction patterns resulting from signal mixing. Because of the scarcity of previous studies on the subject, we adopted a strictly bottom-up approach, with no prior hypotheses regarding the direction or the localization of differences. Only first-episode patients were included, in order to minimize the confounding effects of cumulated antipsychotic exposure and illness chronicity.

Methods
The present investigation was part of a larger study investigating resting-state and task-related brain connectivity in schizophrenia by means of EEG, MEG, and simultaneous electroencephalography-functional magnetic resonance imaging (EEG/fMRI). Participants were 22 patients with first-episode schizophrenia and 22 healthy controls. Patients were recruited through the Psychosis Centre of the Department of Psychiatry of the University Medical Center Hamburg-Eppendorf. First-episode status was defined as having received the first diagnosis and psychiatric treatment less than a year prior to study participation, and presence of psychotic symptoms in any form for no more than 5 years. Healthy controls were recruited from the community. Exclusion criteria for all participants were current substance abuse or dependence, and presence of major somatic or neurological disorders. For healthy control subjects, additional exclusion criteria were any previous psychiatric disorder or treatment, and a family history of psychotic disorders. The presence of inclusion/exclusion criteria was assessed by means of a semistructured interview. The study was conducted in accordance with the Declaration of Helsinki. All participants were required to sign an informed consent form prior to entering the study.

Diagnosis of schizophrenia in patients was established with the Mini International Neuropsychiatric Interview. Severity of clinical symptomatology was assessed with the Positive and Negative Syndrome Scale (PANSS). Because participation in the original project included 3 to 5 neurophysiological testing sessions (EEG, MEG and EEG/fMRI), it was not always possible to conduct clinical assessments close to the EEG session. Therefore,
based on reported trajectories of antipsychotic treatment response.\textsuperscript{50,51} Clinical severity ratings were used for analyses only if they were separated from EEG analyses by no more than a week for acutely ill patients, or 2 months for stable patients (ie, those with no change in medication for at least 2 months prior to study participation). Appropriate clinical ratings were available for 19 patients. Thus, although connectivity analyses were conducted on the entire sample of 22 patients, follow-up analyses on associations with symptoms were based on this subsample of 19 patients.

The majority of patients (18/22) received antipsychotic medication at the time of participation in the study (amisulpride \(n = 1\), aripiprazole \(n = 3\), olanzapine \(n = 5\), paliperidone \(n = 3\), quetiapine \(n = 2\), or risperidone \(n = 5\)). Moreover, 6 patients were currently in treatment with antidepressants. No subjects were receiving benzodiazepines or anticholinergic agents. Demographic characteristics of the 2 groups, and clinical characteristics of patients, are presented in Table 1.

### EEG Recording and Connectivity Analyses

Recordings took place in a sound-attenuated and electrically shielded room. Continuous EEG activity was recorded while subjects were seated comfortably with their eyes closed. Participants were monitored for electroencephalographic signs of drowsiness\textsuperscript{53} for the whole duration of the recording (5–10 minutes). Recordings were conducted at a sampling rate of 1000 Hz with 64 Ag/AgCl electrodes mounted on an elastic cap (ActiCaps; Brain Products, Munich, Germany), using the Brain Vision Recorder software version 1.10 (Brain Products). Eye movements were recorded with 4 EOG channels. Electrode impedance was always kept below 5 k\(\Omega\).

Offline preprocessing was performed with Analyzer 2.0 (Brain Products). A 0.1–70 Hz Butterworth zero-phase bandpass filter (12 dB/octave) was applied. Ocular and prominent muscle artifacts were removed by means of independent component analysis. Subsequently, the recording was divided into 2-second epochs, which were visually inspected for artifacts, recomputed against the average reference, and down-sampled to 256 Hz.

All further analyses were performed in Matlab (Mathworks) using custom-made scripts. Spectral estimates were derived in successive temporal windows of 0.125-second duration with 75% overlap, centered around a frequency of 40 Hz (frequency resolution = 8 Hz), such as to correspond to the frequency range most frequently investigated in previous EEG studies (30–50 Hz). Although abnormalities at higher gamma-band frequencies (60–90 Hz) have also been reported in schizophrenia (see Introduction), all but one of the respective studies have used MEG recordings, which provide a higher signal-to-noise ratio than EEG.\textsuperscript{54} Therefore, and due to practical considerations regarding possible contamination by remaining subtle muscle artifacts, we did not investigate connectivity in these frequencies.

The intracortical sources of brain electrical activity were localized using exact low-resolution electromagnetic tomography (eLORETA).\textsuperscript{55} Head surface EEG data were recomputed into 80 source model time series, corresponding to the centers of all regions of the Automated Anatomic Labeling atlas covering cortical areas and the hippocampi (40 for each hemisphere, see Table 2 for coordinates of each point). Thus, connectivity analyses were based on (80 \(\times\) 79/2\() = \) 3160 pairs of sources distributed throughout the cortex, sufficient for obtaining detailed estimates of connectivity within the constraints posed by the limited spatial resolution of EEG.

As a measure of functional connectivity, we used power envelope correlation between orthogonalized signals,\textsuperscript{46} a measure that addresses the well-known problem of spurious correlation patterns caused by signal mixing, by removing same-phase signal components before calculating power envelopes and their correlation. Measures based on temporal correlations between the amplitude envelopes of neural oscillations have been increasingly used to investigate functional connectivity.\textsuperscript{56–63} It has been suggested that such connectivity measures are conceptually more similar to those obtained with fMRI than coherence-based methods.\textsuperscript{56} It has indeed been shown that amplitude envelope correlations in various frequency bands (including the gamma band) adequately reflect interactions within and between resting-state networks depicted by fMRI.\textsuperscript{39,40,56}

Details of EEG electrode placement and computation methods can be found in the supplementary methods.

### Statistical Analyses

Differences between the 2 groups regarding gamma-band power at the scalp level were assessed with an independent

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**Table 1. Sociodemographic and Clinical Characteristics of the 2 Participant Groups**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Healthy Controls</th>
<th>Schizophrenia</th>
<th>t/(\chi^2)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (m/f)</td>
<td>N/17/5</td>
<td>N/19/3</td>
<td>0.611</td>
<td>.43</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>24.35 (5.1)</td>
<td>24.09 (5.1)</td>
<td>0.165</td>
<td>.87</td>
</tr>
<tr>
<td>Antipsychotic medication dose(^{a})</td>
<td>—</td>
<td>188.64 (181.0)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Total PANSS scores</td>
<td>—</td>
<td>56.00 (15.6)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>—</td>
<td>15.28 (7.9)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>—</td>
<td>14.28 (5.4)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Disorganization</td>
<td>—</td>
<td>15.17 (4.3)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Excitement</td>
<td>—</td>
<td>13.89 (4.9)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Distress</td>
<td>—</td>
<td>17.89 (6.3)</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

\(^{a}\)Chlorpromazine equivalent dose.\textsuperscript{52}
samples $t$ test. At the source level, difference scores were calculated for eLORETA current density power at each one of the 80 cortical points, and the nonparametric randomization approach\textsuperscript{64} was used to estimate critical probability thresholds, corrected for multiple comparisons. The same analysis was applied on the average connectivity values between each cortical point and the rest of the brain.

The above analyses should identify regions of increased or decreased connectivity in patients compared to control subjects, but they do not allow inferences as to what these regions interact with, ie, as to which networks are affected. Therefore, we also used the network-based statistic (NBS) introduced by Zalesky et al.\textsuperscript{65} which corresponds to an application of cluster-based thresholding of statistical parametric maps\textsuperscript{64,66} to the graph model. NBS analyses were conducted using the open-source toolbox NBS Connectome v1.2 (http://www.nitrc.org/projects/nbs, last accessed on Aug 8, 2014). Because contrasts were conducted in 2 directions (controls > patients and vice versa), the significance level was set to 0.025.

A detailed account of the procedures described above is provided in the supplementary methods.

**Results**

The number of artifact-free epochs did not significantly differ between patients and controls (mean $217.3 \pm 52.97$ vs $212.6 \pm 53.47$, $t = 0.326$, $P = .75$). There were no differences between patients and controls regarding either scalp- or source-level gamma-band power (both $P > .7$).

Patients with schizophrenia exhibited significantly increased mean connectivity compared to controls.
C. Andreou et al

in the left rolandic operculum (mean difference score 0.047 ± 0.019, corrected \( P = .045 \)). NBS revealed a network of increased connectivity in patients compared to controls (threshold \( t = 2.8 \), corrected \( P = 0.025 \)). This network involved 33 regions and was composed of 82 connections, mainly of left lateral parietal and temporal areas (including auditory and language areas) with lateral and orbital frontal areas of the same, but also of the contralateral hemisphere (see figure 1 and table 3). The reverse contrast did not identify any networks with reduced gamma-band connectivity in patients (\( P > .4 \)).

The inclusion of antipsychotic medication dose (in chlorpromazine equivalents) did not substantially alter the results.

Alterations of gamma-band activity have been associated with positive and disorganization symptoms in previous studies.\(^{16,17,19,22,31,32}\) Therefore, we conducted exploratory analyses to assess the effect of these symptoms, as follows: We split the patient sample at the median score of the respective PANSS factors\(^{67}\) and used univariate ANOVAs to compare mean connectivity within the network revealed as significant in the above analyses among the 2 resulting (high- vs low-symptom) patient subgroups and healthy controls (see figure 2). For disorganization symptoms, the overall ANOVA was significant \( [F(2,38) = 22.26, P < .001] \). Post hoc tests with Bonferroni correction indicated that patients with low symptoms (PANSS factor score <14, \( n = 9 \)) displayed significantly higher mean connectivity compared to healthy controls (\( P = .002 \)), while high-symptom patients fell in the middle between the other 2 groups (\( P > .09 \) in the comparison to controls, \( P > .5 \) in the comparison to low-symptom patients). However, the effect of positive symptoms disappeared when the 2 factors (positive and disorganization symptom load) were entered simultaneously as fixed factors in a single univariate ANOVA, whereas the effect of disorganization symptoms remained significant \( [F(2,36) = 19.49, P < .001] \).

The observed pattern of results remained essentially unchanged when the above analyses were repeated for the patient group only, including antipsychotic medication dose (in chlorpromazine equivalents) as a covariate.

**Discussion**

The present study investigated resting-state functional connectivity in the gamma frequency range in a sample of first-episode patients with schizophrenia compared to healthy controls. Connectivity changes were analyzed at the neuronal source level. Our analysis revealed increased connectivity within a network comprising mainly left inferior frontal/orbitofrontal, lateral and medial temporal, and inferior parietal areas. Within this network, gamma-band connectivity was higher in patients with low positive and disorganization symptom levels.

The gamma-band connectivity increase in patients observed here contrasts to findings of previous
Table 3. Brain Regions Comprising the Network of Increased Gamma Connectivity in Patients Compared to Controls, Sorted According to Their Degree (Number of Connections) Within the Network

<table>
<thead>
<tr>
<th>Region</th>
<th>Hemisphere</th>
<th>Degree</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angular gyrus</td>
<td>Left</td>
<td>15</td>
</tr>
<tr>
<td>Rolandic operculum</td>
<td>Left</td>
<td>12</td>
</tr>
<tr>
<td>Medial orbitofrontal cortex</td>
<td>Left</td>
<td>11</td>
</tr>
<tr>
<td>Inferior temporal gyrus</td>
<td>Left</td>
<td>9</td>
</tr>
<tr>
<td>Inferior frontal gyrus, pars triangularis</td>
<td>Left</td>
<td>8</td>
</tr>
<tr>
<td>Superior frontal gyrus, orbital part</td>
<td>Left</td>
<td>8</td>
</tr>
<tr>
<td>Postcentral gyrus</td>
<td>Left</td>
<td>8</td>
</tr>
<tr>
<td>Precentral gyrus</td>
<td>Left</td>
<td>8</td>
</tr>
<tr>
<td>Middle temporal gyrus</td>
<td>Left</td>
<td>8</td>
</tr>
<tr>
<td>Middle cingulate cortex</td>
<td>Right</td>
<td>7</td>
</tr>
<tr>
<td>Supplementary motor area</td>
<td>Right</td>
<td>7</td>
</tr>
<tr>
<td>Paracentral lobule</td>
<td>Left</td>
<td>6</td>
</tr>
<tr>
<td>Middle cingulate cortex</td>
<td>Left</td>
<td>5</td>
</tr>
<tr>
<td>Paracentral lobule</td>
<td>Left</td>
<td>5</td>
</tr>
<tr>
<td>Middle orbitofrontal cortex</td>
<td>Left</td>
<td>4</td>
</tr>
<tr>
<td>Heschl gyrus</td>
<td>Left</td>
<td>4</td>
</tr>
<tr>
<td>Supplementary motor area</td>
<td>Left</td>
<td>4</td>
</tr>
<tr>
<td>Supramarginal gyrus</td>
<td>Left</td>
<td>4</td>
</tr>
<tr>
<td>Superior temporal gyrus</td>
<td>Left</td>
<td>4</td>
</tr>
<tr>
<td>Anterior cingulate cortex</td>
<td>Left</td>
<td>3</td>
</tr>
<tr>
<td>Inferior frontal gyrus, orbital part</td>
<td>Left</td>
<td>3</td>
</tr>
<tr>
<td>Superior frontal gyrus</td>
<td>Right</td>
<td>3</td>
</tr>
<tr>
<td>Gyrus rectus</td>
<td>Left</td>
<td>3</td>
</tr>
<tr>
<td>Anterior cingulate cortex</td>
<td>Right</td>
<td>2</td>
</tr>
<tr>
<td>Superior frontal gyrus</td>
<td>Left</td>
<td>2</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>Left</td>
<td>2</td>
</tr>
<tr>
<td>Parahippocampal gyrus</td>
<td>Left</td>
<td>2</td>
</tr>
<tr>
<td>Inferior parietal lobule</td>
<td>Left</td>
<td>2</td>
</tr>
<tr>
<td>Inferior frontal operculum</td>
<td>Left</td>
<td>1</td>
</tr>
<tr>
<td>Inferior frontal gyrus, orbital part</td>
<td>Right</td>
<td>1</td>
</tr>
<tr>
<td>Medial orbitofrontal cortex</td>
<td>Right</td>
<td>1</td>
</tr>
<tr>
<td>Middle orbitofrontal cortex</td>
<td>Right</td>
<td>1</td>
</tr>
<tr>
<td>Gyrus rectus</td>
<td>Right</td>
<td>1</td>
</tr>
</tbody>
</table>

Task-related studies, suggesting that the pattern of gamma-band interactions might differ between rest and conditions of cognitive or sensory stimulation. The only other existing study that assessed source-level resting-state gamma-band connectivity in schizophrenia did not find any significant differences between patients and controls. However, that study did not use signal orthogonalization to minimize the effects of volume conduction. Perhaps more importantly, the connectivity measure used was based on phase synchronization, whereas the present study used an amplitude-based measure of connectivity. It has been suggested that the 2 types of measure may reflect different underlying coupling mechanisms and their function, which could explain differences between the 2 studies.

The increase of gamma-band connectivity was not unspecific, but rather involved a distinct and strongly lateralized network. The latter comprised areas relevant for language and memory functions, which have been reported to be affected in schizophrenia, and in disorganization both in auditory hallucinations and in disorganization symptoms. Thus, the present results may provide a link between aberrant gamma-band connectivity at rest and core clinical symptoms of schizophrenia.

However, the suggested link of aberrant gamma-band coupling with symptoms is not a straightforward one: Patients with higher disorganization and positive symptom scores actually exhibited lower mean connectivity values within the affected network. Interestingly, a similar pattern has been reported in previous task-related studies of gamma-band oscillations: Although both the stimulus-locking of local gamma-band phase and the long-range synchrony of gamma oscillations are reduced in patients with schizophrenia, their correlation with positive symptoms is a positive one. In contrast, a study that reported an increased delayed left-hemisphere gamma-band response to speech in patients with schizophrenia found a negative correlation with hallucination severity. All the above findings indicate that increased psychopathology is associated with more “normal” measures of local phase-coupling and/or interregional synchronization in the gamma frequency range. This appears counter intuitive, but a look into the physiological role of gamma oscillations in normal cognition might help elucidate this discrepancy. It has been suggested that gamma-band oscillations mediate the integration of stimuli according to previous predictions, and possibly also the suppression of inappropriate associations. For example, gamma-band oscillations increase in response to highly predictable words within a sentence; they have also been associated with suppression of the formation of inappropriate memories in rats and with the suppression of phantom perceptions such as tinnitus. Although the above findings refer to local gamma-band power, recent evidence suggests that they may apply to long-range functional connectivity as well (which would be more relevant for the present study). For example, a recent psycholinguistic study has suggested that gamma-band coherence between frontal and posterior areas might mediate the matching between incoming stimuli and pregenerated semantic expectations.
which however is too severe to be incorporated into such an explanatory network and produce symptoms (see Whitford et al. for a similar interpretation of diffusion tensor imaging abnormalities in schizophrenia). These 2 explanations lead to opposite hypotheses regarding the changes of gamma-band abnormalities over the course of clinical improvement: If increased gamma-band coupling represents a successful compensatory mechanism, it should increase over the course of clinical improvement in acutely ill subjects. However, if it reflects a primary abnormality, it should show little change or even decrease parallel to symptom decline. Unfortunately, the cross-sectional nature of the present study precludes a definite conclusion as to which of the 2 assumptions holds. Longitudinal studies of patients over the course of clinical improvement, or studies of individuals at high-risk for psychotic disorders, are warranted to provide an answer to this question. Another interesting question to be addressed in future studies is how abnormal large-scale connectivity in the gamma band relates to task-related local synchronization deficits observed in patients, and how this association might be influenced by symptom severity.

Of note, increased connectivity in patients was observed in the absence of gamma-band power abnormalities, confirming that the 2 measures can be differentially affected. The finding of normal resting-state gamma-band power in patients is in apparent discordance with several reports of baseline gamma-band power increase in schizophrenia. However, all of these studies have used prestimulus gamma-band power in the context of sensory stimulation paradigms as a measure of “resting-state” gamma-band activity, and in one case the authors argued that the enhanced baseline gamma-band activity might have been a result of multiple stimulus presentation. On the other hand, 3 studies assessing resting-state gamma-band power in a manner similar to the present study reported no differences between patients with schizophrenia and control subjects, or even decreased gamma-band power in patients.

Certain limitations of the present study need to be addressed. First, most patients were currently receiving antipsychotic medication. Any direct effects of antipsychotic medication are rather unlikely in the present study because chlorpromazine equivalent dose had no effect on results. Moreover, preliminary evidence suggests that medication status does not affect neural oscillations in general, nor gamma-band oscillations in particular. On the other hand, we cannot exclude the possibility that the changes observed (especially in low-symptom patients) were mediated by the effects of antipsychotic treatment. Antipsychotic medication has indeed been reported to affect fMRI connectivity patterns in patients with schizophrenia. As already mentioned above, longitudinal studies are required to shed light on these questions. Second, although EEG has several advantages when it comes to assessing fast neural network dynamics and the precise coordination of oscillations at different frequencies, it is limited both in its spatial resolution and in its capacity to detect sources of electrical activity at deep locations and in the cerebellum. Thus, the present results do not yield information on possible changes in structures such as the amygdala, thalamus, basal ganglia, and cerebellum, all of which have been implicated in connectivity disturbances in schizophrenia. A cautionary note is also appropriate with regard to the chosen method of functional connectivity calculation: Although methods based on excluding...
same-phase signal components are currently the only available way of dealing with spurious interaction patterns due to signal mixing, and although these methods generally reveal connectivity structures much more clearly than uncorrected measures, it should be kept in mind that this approach also discards true zero-phase interactions that are known to exist in the brain. Finally, although the present study focused on the gamma band, oscillations of other frequency ranges have been also implicated in the pathophysiology of schizophrenia. Especially theta-band oscillations are of interest, as evidence suggests that they are also dependent on the parvalbumin-positive interneuron system and that theta- and gamma-band oscillations display significant interactions. In light of these findings, studies on cross-frequency coupling between theta- and gamma-band oscillations would be of particular relevance for understanding the pathophysiology of schizophrenia.

In summary, the present study provides a link between abnormal resting-state gamma-band connectivity and the core symptoms of schizophrenia, although further work is needed to clarify the nature of this association. Thus, our results confirm that investigations of the resting state in schizophrenia might disclose new aspects regarding the pathophysiology of the illness, complementing findings by task-based studies.

Supplementary Material
Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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