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ORIGINAL PAPER

Alterations in resting-state gamma activity in patients with schizophrenia: a high-density EEG study

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Abstract

Alterations of EEG gamma activity in schizophrenia have been reported during sensory and cognitive tasks, but it remains unclear whether changes are present in resting state. Our aim was to examine whether changes occur in resting state, and to delineate those brain regions where gamma activity is altered. Furthermore, we wanted to identify the associations between changes in gamma activity and psychopathological characteristics. We studied gamma activity (30–48 Hz) in 60 patients with schizophrenia and 76 healthy controls. EEGs were acquired in resting state with closed eyes using a high-density, 256-channel EEG-system. The two groups were compared in absolute power measures in the gamma frequency range. Compared to controls, in patients with schizophrenia the absolute power was significantly elevated (false discovery rate corrected $p < 0.05$). The alterations clustered into fronto-central and posterior brain regions, and were positively associated with the severity of psychopathology, measured by the PANSS. Changes in gamma activity can lead to disturbed coordination of large-scale brain networks. Thus, the increased gamma activity in certain brain regions that we found may result in disturbances in temporal coordination of task-free/resting-state networks in schizophrenia. Positive association of increased gamma power with psychopathology suggests that altered gamma activity provides a contribution to symptom presentation.

Keywords Schizophrenia · Gamma activity · Resting state

Introduction

Gamma oscillation is considered to be essential for the synchronization of large-scale neuronal networks, and to provide the basis for consciousness, and cognitive and perceptual functions [1]. Electrophysiological studies found impairments in individuals with schizophrenia in gamma band (> 30 Hz) oscillations (GBO) [2]. Furthermore, post-mortem studies of patients with schizophrenia found changes in GABAergic and glutamatergic systems [3], which may be involved in the generation of GBO [4]. Neurodevelopmental data suggest that such alterations may occur during brain maturation, which is consistent with the view that schizophrenia is a neurodevelopmental disorder [5]. Altered synchronization of large-scale brain networks may result in disturbed connection between distinct brain regions, suggesting a dysconnectivity in neural operations in schizophrenia [6, 7]. Moreover, impairment in cognitive and perceptual functions has been reported in schizophrenia [8]. Thus, it is conceivable that disturbed GBO may play a role in the pathophysiology of the disorder.

GBO can be investigated by non-invasive EEG recordings in various task situations or in resting state. Former studies confirmed that sensory-evoked gamma response is reduced in patients with schizophrenia compared to healthy controls [9–23]. Furthermore, in cognitive tasks, reduction of gamma response was found in patients with schizophrenia compared to controls in selective attention [9, 24–26] and working memory tasks [27–30]. These task-related gamma disturbances were mostly reported in lower gamma frequency range 30–50 Hz, especially around 40 Hz [22, 23, 31]. Much work has been devoted to investigations with sensory-evoked and cognitive paradigms, however, resting-state gamma activity has been rarely studied [32–38].

Recent resting-state studies, using fMRI, showed evidence that task-free/resting-state networks correlate with task-positive networks. A recently published study, which

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focused on individual differences in resting state, created a model that can predict task-specific activation from task-independent fMRI measurements collected at rest [39]. The hypothesis, that resting-state gamma activity is altered in schizophrenia is supported by the facts that in patients with schizophrenia alterations of GBO were observed during various tasks, and that there is a correlation between task-positive networks and task-negative networks in fMRI [39].

EEG studies that applied resting-state paradigms to compare patients with schizophrenia and healthy controls reported altered absolute power of high-frequency activity including the beta and gamma ranges, but the results are heterogeneous. Furthermore due to the inclusion of beta range, it is unclear whether these high-frequency alterations appeared in beta or gamma range. Several studies found elevated high-frequency activity in patients with schizophrenia compared to healthy controls, but most of them investigated frequencies only up to 40 Hz [40–45]. The results of studies focusing exclusively on gamma frequencies suggested elevated gamma activity at rest; however, the scalp distribution of these alterations has remained largely unexplored. They mostly reported elevated gamma power in patients with schizophrenia [33–38, 46, 47], although one study [32] found no difference between the study groups in terms of gamma power. We note that a MEG study reported no difference, and another found decreased gamma power [48, 49]. Most of the research groups focused on 30–50 Hz gamma range.

A common feature of these studies was that they were based on the analysis of wide scalp areas, not considering that these regions encompass distinct brain areas of different functional significance. Furthermore, the division of sensor locations according to topographical regions varied across studies, which decreases the generalizability of the results. A few studies used high-density EEG recording [35–38]. Nonetheless, they collapsed their data according to broad brain regions despite the fact that with a sensor-based analysis of the high-density EEGs, topographic distribution of alterations could be more reliably described.

The present study investigated differences in spontaneous gamma activity in patients with schizophrenia and healthy controls (HC). We used high-density EEG to delineate those brain areas in detail where alterations in gamma activity are manifested and may reflect the operation of networks activated at rest. Focusing on the gamma frequency range of 30–48 Hz that was identified by previous studies [22, 23, 31], we performed a comprehensive, sensor-based analysis of gamma power differences including the full sensor space of 256 channels to identify brain areas that may be associated with those networks that contribute to the pathophysiology of schizophrenia. Furthermore, we investigated the association of gamma activity with psychopathological and clinical measures.

Methods and materials

Participants

60 patients with schizophrenia (mean age = 35.2 years (SD = 9.6), male percentage = 51.6%) and 76 healthy controls (HCs) (mean age = 32.3 years (SD = 10.6), male percentage = 35.5%) participated in the study. Patients were recruited from the Semmelweis University Department of Psychiatry and Psychotherapy, Budapest, Hungary. The inclusion criteria were age (18–65 years), and diagnosis of schizophrenia according to the International Classification of Diseases (ICD-10). Exclusion criteria were any kind of neurological disorder, serious head injury (with loss of consciousness > 5 min) and substance abuse at the time of testing. HCs were recruited from a community sample through medical staff of the University and friends. Inclusion criteria were age (18–65) years and exclusion criteria were history of, or current neurologic or psychiatric diseases.

All participants provided written informed consent and the study was approved by the Scientific and Research Committee of the Medical Research Council in Budapest, Hungary. The authors assert that all procedures contributing to this work comply with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Electrophysiological data collection and processing

EEGs were recorded by the 256-channel Biosemi Active Two system (Biosemi Inc., Amsterdam, Netherlands) at a sampling rate of 512 Hz, referenced to the vertex. The signal was bandpass-filtered on-line (0.1–100 Hz). Electro-oculogram (EOG) was recorded for monitoring eye movements for artifact identification. Participants sat in a dimly lit room, and were asked to remain still with eyes closed for 2 min.

The recorded data were further processed offline with MATLAB EEGLAB toolbox [50]. EEG was re-referenced to the common average potential, and filtered off-line (bandpass = 1–100 Hz) using zero-phase shift-forward and reverse-IIR Butterworth-filter. A 48-52Hz Parks-McClellan stop-band Notch-filter in ERPLAB [51] was used to remove electric-interference from the 50 Hz-line.

EEG data were manually inspected and non-brain-related artifacts such as muscle contractions and movement-related artifacts were removed. This cleaning procedure resulted in an average 94.35 (SD = 16.36) and 94.53 (SD = 14.67) seconds of data for controls and patients with schizophrenia, respectively. Furthermore, an Independent Component Analysis (ICA)-based method was used

with ADJUST toolbox to eliminate the remaining muscle and eye movement-related artifacts [52]. ICA provides a method for correcting EEG signal, since it may effectively eliminate ocular artifacts which may have been overlooked in the manual- and threshold-based artifact rejection procedures [53]. Subsequent analysis was performed on 60 s of artifact-free EEG data, according to its reliability in resting-state EEG power spectra [54].

On the corrected EEG data FFT was performed to extract absolute power based on Welch's method, using a 2-s, 75% overlap window [55] and 0.5 Hz frequency bin resolution. Gamma band power was calculated in 31–48 Hz, by the summation of absolute power on frequency bins within the specified frequency range. Log10 transform was computed for the summed frequency band, which yielded a better approximate of normal distribution compared to the raw data.

Psychometric and clinical measures

We collected psychometric and clinical variables to examine their relationship with spontaneous gamma activity. The total and the five factor scores of Positive and Negative Symptoms Scale (PANSS) were used to characterize psychopathology [56], which was available in a subset of patients ($n=42$). Chlorpromazine (CPZ) equivalent daily doses of antipsychotic medications were calculated for each patient [57, 58]. HCs were screened using the Symptom Checklist-90-Revised (SCL-90-R) scale, a self-report instrument to evaluate a broad range of psychopathology [59].

Statistical analysis

The primary statistical analysis for group-differences between patients with schizophrenia and HCs was based on the random regression hierarchical linear model (HLM). We conducted our analysis for the absolute power, which served as dependent variable in the HLM. Group was used as an independent variable. Gender, age, and education level were used as covariates to adjust for potential confounding by these variables. We performed a channel-wise comparison between patients with schizophrenia and controls. We applied the Hochberg procedure for correction for multiple testing [60]. For those channels where significant group-differences emerged after correction, we conducted additional statistical analysis to explore the relationship of psychopathological and clinical variables with gamma power changes in patients. The latter analysis was performed for the schizophrenia group, using the following variables: PANSS total score (for subset of patients), benzodiazepine (BZD) medication (yes/no) and CPZ equivalent daily dose (mg/day). Finally, in a subsidiary analysis we investigated which frequencies are dominantly presented in the alterations in schizophrenia we found in the gamma range. For this purpose, we computed the spectral centroid in the gamma band, which is considered as a measure of the center frequency for a given range of the frequency spectrum [61]. It is calculated as the weighted mean of the frequencies in the spectrum, weighted by their magnitude/spectral power. We derived the spectral centroid frequency in the gamma range for each participant in both groups. We averaged the resulted frequency bins across channels for each individual. Specifically, we conducted two analyses to compare the groups: one for the average of centroid frequencies for all electrodes (256) over the entire scalp and one for the average of only those electrodes which exhibited a between-group difference in absolute power in our analyses. SAS 9.4 software was used for statistical analysis.

Results

Demographics and basic descriptive statistics

Demographic and clinical data of study participants are presented in Table 1. There were no significant between-group differences in terms of age ($F=2.66$; $p=0.1$), gender ($\chi^2=2.27$; $p=0.13$) and education level ($\chi^2=0.81$; $p=0.36$). While the analysis for age yielded a marginally significant p value due to the large sample size, the difference was less than 3 years between the study groups. Patients compared to HCs attained lower education, which is an accompanying characteristic of schizophrenia disorder [62]. Nonetheless, we used these characteristics as covariates to adjust for potential confounding by these variables.

Group difference in absolute gamma power

Our findings indicated elevated gamma activity in patients with schizophrenia at rest. In terms of nominal significance, 118 out of 256 channels showed significantly elevated gamma power in patients with schizophrenia compared to healthy controls. A total of 78 channels of these remained significant after correction for multiple comparisons. The topographical distribution of absolute gamma power by study groups, and the group differences are shown in Fig. 1. As shown by the figure, the group differences emerged in two topographical areas, enclosing a fronto-central and posterior clusters. The fronto-central cluster comprised 29 channels (minimum nominal F value $=6.11$; $p=0.0147$; maximum nominal $F=15.89$; $p=0.0001$). The posterior cluster comprised 49 channels (minimum F nominal value $=7.15$; $p=0.0085$; maximum nominal $F=18.02$; $p<0.0001$).

Table 1 Demographic and clinical characteristics

Characteristics	Schizophrenia group ($n=60$)	Healthy controls group ($n=76$)	Test statistics	
			Chi-square test	p value
Categorical variables (N)				
Gender (n, male/ female)	29/31	27/49	2.27	0.13
Education level ($n1/n2$)[a]	46/14	53/23	0.81	0.36
Benzodiazepine usage yes/no	38/22	–[c]	–[c]	–[c]
Characteristics	Schizophrenia group ($n=60$)	Healthy controls group ($n=76$)	Test statistics	
			ANOVA (F)	p value
Continuous variables: mean (SD)				
Age (years)	35.2 (9.6)	32.3 (10.6)	2.66	0.1
PANSS total score[b]	87.6 (17.91)	–[c]	–[c]	–[c]
Positive score	20.23 (6.41)	–[c]	–[c]	–[c]
Negative score	23.71 (4.89)	–[c]	–[c]	–[c]
General score	43.71 (9.55)	–[c]	–[c]	–[c]
CPZ—chlorpromazine equivalent daily dosage	599 (333.47)	–[c]	–[c]	–[c]
Illness duration (years)	10.1 (8.57)	–[c]	–[c]	–[c]

[a]$n1$, without college degree; $n2$, College/University degree

[b]Obtained for 42 patients

[c]*NA* not applicable

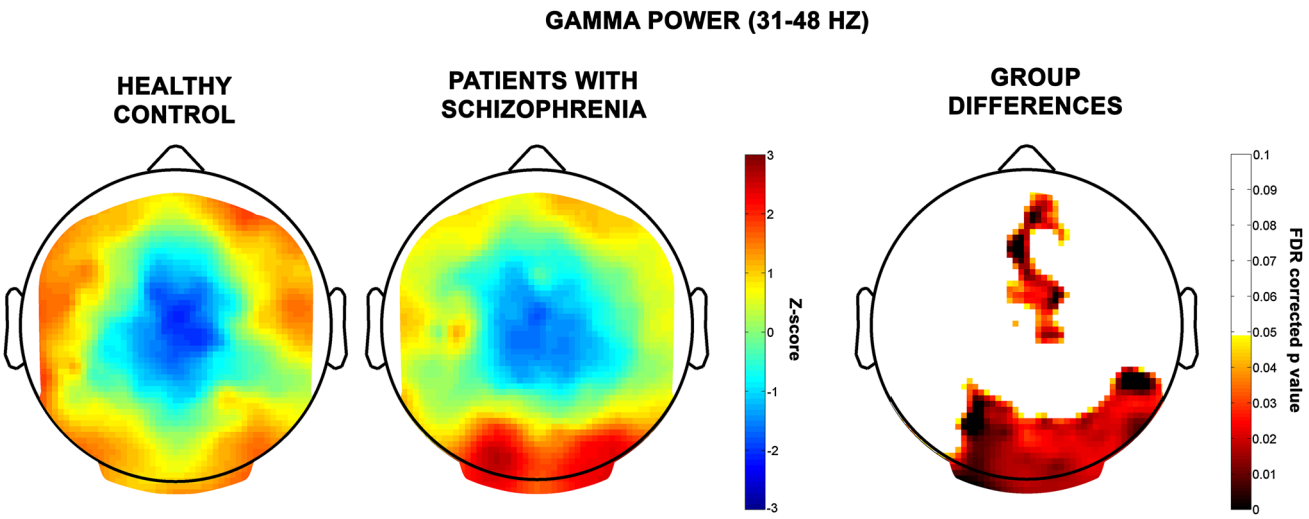

Fig. 1 Topographic maps of absolute gamma power (frequency range 30–48 Hz) in patients with schizophrenia and healthy controls (left two columns) along with the statistical parameter map of group-differences (rightmost column). The color bar indicates z-scores, computed based on gamma power in each individual channels across the scalp. In the rightmost column, we illustrate the scalp topography of group differences, where increased absolute gamma power in patients reached statistical significance (color coding indicates FDR-corrected p values)

Group difference in mean frequency of gamma changes

Our analyses indicated that, while there was a group difference in spectral power as detailed above, the power distribution across the gamma frequency range was similar in the two groups. Specifically, in terms of analyses based on data from all 256 electrodes over the scalp, we found no significant difference in the frequency distribution in the gamma range between the two groups ($F=1.18$; $p=0.28$). The mean frequencies were 36.9 Hz (SD = 0.42 Hz) and 36.8 Hz (SD = 0.66 Hz) for the healthy controls and patients with

schizophrenia, respectively. Similarly, we found no difference in the frequency distribution when we examined only those electrodes in our analyses which exhibited a between-group difference described in the previous section [the mean frequencies were 36.9 Hz (SD = 0.40 Hz) and 36.8 Hz (SD = 0.64 Hz) in the control and schizophrenia group, respectively ($F = 1.28$; $p = 0.26$ for the group difference)].

Relationship of symptom severity with gamma power

To explore the relationship between psychopathology and gamma alterations, we performed additional analyses based on the clusters of channels in fronto-central and posterior regions. We found significant interaction effects in three PANSS measures (total score, negative and hostility factor) in the posterior region between the scalp location and symptom severity, which indicated that increase in gamma activity with symptom severity varied across the channels in the posterior scalp location ($F = 2.38$; $p < 0.0001$, $F = 1.64$; $p < 0.0037$ and $F = 3.86$; $p < 0.0001$, respectively). Based on these interactions, we further investigated which channels in this scalp area contributed significantly to the associations, and found that these channels were located over the left occipital cortex. Higher symptom severity, as measured by the PANSS total score, showed significant relationship with increased gamma power in 13 (out of 49) channels. We further analyzed the five factors of PANSS, where higher negative and hostility factor scores showed significant relationship with increased gamma power in 11 and 15 (out of 49) channels, respectively. All these channels covered the left occipital cortex. Results are presented in Table 2.

We found no significant relationship between gamma power and CPZ equivalent dosages. In addition, there was no difference in gamma power ($p > 0.05$ in all analyses) between subjects who used or did not use benzodiazepine, respectively.

Discussion

Our aim was to examine whether there is a difference in resting-state EEG gamma activity between patients with schizophrenia and HCs. We found an increase of gamma power in patients with schizophrenia, and the detailed regional analysis indicated a topographically specific increase of absolute gamma power in patients compared to HCs which encompassed the fronto-central and parieto-occipital regions.

Alterations in gamma activity may lead to disturbed functional connectivity in brain networks, which may be interpreted as further evidence for the cortical dysconnectivity hypothesis of schizophrenia [2, 7]. Since fMRI studies suggest a low-frequency network operation in resting-state, it is conceivable that fast-frequency activity, such as gamma, could modulate these operations and, therefore, contributes to the functionality of these networks. Increased GBO may interfere with large-scale brain network operations; thus, our findings may be manifestations of altered connectivity of such brain networks and may reflect dysconnectivity in schizophrenia, thereby contributing to symptom presentation [6, 63–76].

Changes in resting-state activity may be an indication of a wide-spread disturbance in the neural operations in schizophrenia, as a relationship between gamma activity alterations in resting-state and task-related activity has been reported in the literature. In particular, in healthy subjects, Tavor et al. [39] found that resting-state activity and task-induced activity are correlated, and from resting-state activity

Table 2 Significant relationship of channels in posterior region with PANSS scores (PANSS total score, negative factor and hostility factor)

PANSS variables	Posterior region (total number of included channels = 49)						
	Number of channels[a]		*F*	*p*	diff	SD	Cohen *d*'
Hostility factor	15	Min	4.11	0.0498	0.59	0.23	0.42
		Max	12.52	0.0011	1.10	0.24	0.74
Negative factor	11	Min	4.13	0.0494	0.50	0.16	0.52
		Max	8.76	0.0054	0.58	0.13	0.76
PANSS total score	13	Min	4.50	0.0407	0.35	0.11	0.50
		Max	10.13	0.0030	0.63	0.14	0.75

Analyses were performed for the individual channels in the posterior region since significant interaction effect in this region between the scalp location and symptom severity appeared. Channels, where significant interaction presented, were located over the left occipital region and denoted by the following labels (according to BioSemi electrode system): 'A9', 'A10', 'A11', 'A12', 'A13', 'A14', 'A15', 'A19', 'H16', 'H18', 'H19', 'H26', 'H27', 'H28', 'H29', 'H30', 'H31', 'H32'. https://www.biosemi.com/pics/cap_256_layout_medium.jpg

[a]Number of channels which was in significant relationship with gamma power. Min/max indicate the minimum and maximum *F* values, where analysis yields significant results

task-induced activity can be predicted. In schizophrenia, task-induced alterations result in reduced gamma activity compared to healthy control subjects [31]. When pre-stimulus baseline power is elevated (which could be resulting from an increased gamma in resting state), it can interfere with gamma activity under task condition. Overall, altered resting-state gamma activity may result in insufficient activation during task performance in schizophrenia, which leads to disturbed neural network activation, a possibility which clearly needs further empirical evaluation.

Gamma disturbances could be the result of deficient brain maturation, which is consistent with several lines of evidence about the neurodevelopmental aspects of schizophrenia, including (1) typical onset of schizophrenia occurs during the transition from late adolescence to adulthood [77]; (2) myelination of long axonal fibers increase during adolescence, resulting in enhanced long-range connectivity [78]; (3) high-frequency oscillations and their synchronization increase during adolescence, which may be related to the re-organization of cortical networks [77]; (4) neurodevelopmental data have highlighted the modification of the amplitude and synchrony of theta-, beta- and gamma-frequencies [79]; and (5) evidence pointing to important modifications in neurotransmitter systems that support high-frequency oscillations [80].

Increased gamma power is consistent with the hypothesis of NMDA receptor (NMDAR) dysfunction in schizophrenia based on several lines of data. Specifically, the use of NMDAR antagonists, such as ketamine, PCP and MK-801, are associated with psychotic symptoms and impairment in cognitive functioning in healthy volunteers [81]. Furthermore, a recent paper showed that glutamate levels in the cortex specifically correlate with evoked gamma-band response during cognition [82]. Additionally, based on animal models of schizophrenia, elevated baseline gamma oscillation has been reported [3]. In vivo local field power (LFP) and EEG recordings of rodents using NMDAR antagonists, including ketamine or PCP, showed enhanced high-frequency oscillations [31]. Finally, important animal models of schizophrenia are based on NMDA system modulation [83, 84]. Overall, the aforementioned findings are consistent with the idea that NMDAR hypofunction in schizophrenia is related to gamma power disturbances, and are in line with the dysconnectivity hypothesis.

There are only a few studies that investigated resting-state gamma activity in schizophrenia, and most of them did not examine topographical distribution [32–34]. Our findings of increased gamma activity are consistent with most prior analyses of resting-state EEG in patients with schizophrenia. In particular, all of these studies applied an eyes-closed resting-state paradigm while investigating gamma activity, albeit they adopted different approaches. One study reported increased resting gamma (40–85 Hz) activity in patients with schizophrenia compared to HCs, although the authors did not specify the scalp regions where group-differences emerged [34]. Another study [33] investigated omega-complexity (OC) as a measure of global coordination of a specified frequency range in resting-state EEG, and found elevated OC in the gamma range (30–50 Hz) in schizophrenia patients, suggesting less coordinated activity in frontal regions. A third study, however, found no significant difference in gamma power between patients with schizophrenia and HCs [32].

Topographical analysis was undertaken by Tikka's group, to investigate gamma activity in schizophrenia as a function of various disease conditions, including minor physical anomalies (MPA), first rank symptoms (FRS), sporadic or familiar occurrence of the disease, and medication status [35–38, 47]. While these authors found elevated gamma activity in schizophrenia patients, there was less consistency with regard to the brain regions and to the specific frequencies within the gamma range where the differences appeared. It is noteworthy that patients with more MPAs had increased gamma power compared to those with less MPAs, suggesting a neurodevelopmental background for gamma alterations [36, 38]. Medication had no impact on gamma power in these studies, suggesting that gamma oscillation disturbance may represent a trait marker in schizophrenia [35].

In our study, we found altered gamma power in patients with schizophrenia compared to HCs, and the detailed regional analysis revealed that group-differences emerged in both anterior and posterior regions. Specifically, elevated gamma activity was found in midline frontal regions with a slight right-lateralization, including channels that may reflect activity of anterior frontal and prefrontal cortical regions. Aberrant resting-state gamma in frontal regions is consistent with prior data, indicating an association between gamma oscillations and neurocognitive deficits in schizophrenia [85, 86]. Differences in posterior regions involve areas of right inferior parietal, left medial parietal and occipital regions in both hemispheres. Parietal regions together with frontal areas form a hetero-modal association cortex, which may be impaired in schizophrenia [87]; elevated gamma in these areas may compromise functional integrity. Increased gamma in occipital areas has been interpreted as a cortical noise, which influences visual perception mechanisms; indeed, disturbed gamma oscillations have been observed in patients with schizophrenia in a visual Gestalt paradigm [23]. In addition, increase in psychopathology as measured by the PANSS showed that this cortical noise in occipital region is associated with more severe psychopathology.

Study limitations include that patients and controls were not individually matched on age, gender and education level. Nevertheless, the group differences were not statistically significant even at the large sample size that we had in the current study, and adjustments for these variables have been

made in the analyses. Further limitation is that the assessment of psychopathology was not available for all patients. While this limitation resulted in a loss of statistical power in the analyses of these variables, we were able to identify associations between gamma activity and symptom severity based on the available data. Similar to most studies, patients were medicated in our study. However, we found no association with medication (including benzodiazepines and antipsychotics) on gamma power in patients with schizophrenia. Nonetheless, we think that further research is needed to clarify this point. Finally, a potential caveat with regard to the interpretation of our findings is the possibility that patients were more "aroused" even during resting state than healthy controls. We think that, on the basis of the arousal assumption, one could expect a uniform distribution for the elevation in gamma power in patients with schizophrenia, which we were not able to detect in this study. In fact, our study identified an increase in gamma power in a topographically specific manner. We thus think that a confounding of our principal findings by the level of arousal is not likely in the current study.

Overall, our findings provide further support for an increase of gamma power in patients with schizophrenia, and for the association of those increases in several brain regions with more severe psychopathology. In view of the findings indicating that changes of high-frequency oscillations may occur during brain maturation [77–80], it is conceivable that neurodevelopmental changes lead to disturbances in gamma activity, which in turn may contribute to the development of schizophrenia. Elevated gamma power may reflect an intrinsic deficit in the temporal coordination of distributed neural activity [88]. The fact that these changes were observable at rest suggests deficient operation of task-free networks in schizophrenia. Because activity of task-negative and task-positive networks is closely related [39], our findings are consistent with the view that functional dysconnectivity of large-scale neural networks may play a role in the psychopathology in schizophrenia.

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Compliance with ethical standards

Conflict of interest None of the authors declared conflict of interest with regard to the study.

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