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REGULAR ARTICLE

Unsuccessful reduction of high-frequency alpha activity during cognitive activation in schizophrenia

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Aims: Electroencephalogram (EEG) alpha activity during resting state reflects the 'readiness' of an individual to respond to the environment; this includes the performance of cognitive processes. Alpha activity is reported to be attenuated in schizophrenia (SCZ). Understanding the interaction between alpha activity during rest and when cognitively engaged may provide insights into the neural circuitry, which is dysfunctional in SCZ. This study investigated the changes of alpha activity between resting state and cognitive engagement in SCZ patients.

Methods: Thirty-four SCZ patients and 29 healthy controls (HC) were recruited. EEG was performed in the resting state and during an auditory P300 task. All experimental procedures followed the relevant institutional guidelines and regulations.

Results: In SCZ, high-frequency alpha activity was reduced in the resting state. High-frequency alpha source density was decreased in both the resting-state and a P300 task condition in patients, compared to HC. HC, but not SCZ patients, showed a reduction in high-frequency alpha source density during the P300 task compared to the resting state. The negative correlation between high-frequency alpha source density in the resting state and positive symptoms was significant.

Conclusions: High-frequency alpha activity in SCZ patients and its unsuccessful reduction during cognitive processing may be biological markers of SCZ.

Keywords: *high-frequency alpha band, high-frequency alpha band reduction, P300, resting-state EEG, schizophrenia.*

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Schizophrenia (SCZ) is characterized by attenuated alpha activity on electroencephalography (EEG) resting condition with eyes closed and open.[1–7] Correlations between EEG alpha activity and positive/negative symptoms of SCZ have also been observed.[5,8,9]

Alpha oscillation is known to reflect physiological arousal and a relaxation state.[10] Resting-state EEG alpha activity is increased during eye-closed conditions compared to eye-open conditions,[11,12] suggesting that the resting-state alpha activity with eyes closed reflects the baseline state of the brain. The appearance of the high-alpha band (10–13 Hz) indicates increased relaxation and a lessening of tension in a wakeful resting condition.[13] Additionally, the EEG alpha wave is known to occur predominantly at the visual cortex, and is associated with the inhibition of sensory stimulation.[14]

The functionality of sensory gating has been demonstrated during the oddball task in SCZ.[15] The auditory paradigm is a reliable cognitive task for investigating sensory modulation, such as cognitive attention and inhibition, because the experimental conditioning is easy and because this paradigm can be designed specifically for studying SCZ.[16–18] Regarding event-related potentials (ERP), when participants focus on a cognitive task, their alpha activity decreases, whereas excitatory neural oscillations increase,[9,12,19] indicating that alpha activity and cognitive brain activations are inversely related. It has been suggested that event-related alpha oscillations indicate brain activity during cognitive loading.[20] Previous studies have reported that a specific band frequency power decreased during task performance or after stimulus onset. This relationship is defined as event-related desynchronization (ERD)[12,21–23] and has been suggested to reflect thalamocortical interaction.[24–26] The analysis of pre-stimulus and post-stimulus ERD in SCZ patients[6] indicates cognitive strategies of adapting to external stimuli.[27] Insufficient cognitive processing in daily life activities represents a major pathology in SCZ, but its biological mechanisms are not fully understood. In particular, evidence on alterations of sensory processing of external events or the absence of events in SCZ is lacking. The role of the change in alpha activity between an eye-closed resting state and a cognitive-load condition in the neurophysiology of SCZ thus remains to be elucidated. Furthermore, there are two possible arguments. First, desynchronization of alpha activity is connected with visual function via the reticular activating system from resting state with eyes closed and open.[28,29] Second, alpha activity reflects modulation of readiness and arousal state, which is dysfunctional in SCZ patients.[30,31] To reflect the neutralized baseline state, we analyzed EEG signals during the resting-state

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condition rather than during the pre-stimulus stage, because stimuli can induce a pre-stimulus/post-stimulus interference effect on the stimulus presented next.

We hypothesized that SCZ patients exhibit less alpha activity than healthy controls (HC) at rest and that HC show more decreased alpha activity than patients during a P300 task than during a resting state, which is indicative of successful or unsuccessful reduction, depending on the dynamics of the neural population. The present study aimed to: (i) investigate whether alpha activity is attenuated in SCZ patients compared to HC; (ii) compare alpha activity between resting-state and cognitive-task conditions (i.e., an auditory P300 paradigm); and (iii) correlate EEG source activity and the clinical symptoms of SCZ.

Methods

Participants

Thirty-four (14 men and 20 women) SCZ patients and 29 (11 men and 18 women) HC were included in this study. HC were selected through public advertising in Seoul, South Korea. Participants with hearing problems, a history of drug and/or alcohol abuse, or a lifetime history of neurological disorders were excluded, based on a questionnaire. HC with any history of psychiatric disorders were also excluded. All smokers were excluded. The mean age of all participants was 42.30 ± 13.46 years (range, 21–69 years). Patients were diagnosed with SCZ based on the Structured Clinical Interview for the DSM-IV, Axis I, psychiatric and personality disorders,[32,33] and were evaluated using the Positive and Negative Syndrome Scale (PANSS) by a trained psychiatrist not directly related to the study.[34] The characteristics of the participants are summarized in Table 1. No group differences in age or sex were observed. Medication states of patients are summarized in Table 2. The present study was approved by the Institutional Review Board of Seoul Saint Mary's Hospital, College of Medicine, Catholic University of Korea. All participants provided signed informed consent. All experimental procedures followed the relevant institutional guidelines and regulations.

Electrophysiological measurement and analysis

Participants were seated in a comfortable chair in a sound-attenuated room. The EEG data were recorded using a NeuroScan SynAmps amplifier (Compumedics USA, El Paso, TX, USA) with a head cap mounted with AgCl electrodes according to the extended International 10–20 system.[35] We recorded from 62 scalp positions (FP1, FPZ, FP2, AF3, AF4, F7, F5, F3, F1, FZ, F2, F4, F6, F8, FT7, FC5, FC3, FC1, FCZ, FC2, FC4, FC6, FT8, T7, C5, C3, C1, CZ, C2, C4, C6, T8, TP7, CP5, CP3, CP1, CPZ, CP2, CP4, CP6, TP8, P7, P5, P3, P1, PZ, P2, P4, P6, P8, PO7, PO5, PO3, POZ, PO4, PO6, PO8, CB1, O1, OZ, O2, and CB2). Additional electrodes were placed above and below the left eye for vertical electrooculography and at the outer canthus of each eye for horizontal electrooculography. The EEG data were recorded with a 1–100-Hz band-pass filter at a sampling rate of 1000 Hz. The signals were referenced to both mastoids where the ground electrode was placed on the forehead. Impedance between electrodes and scalp was maintained below 5 kΩ during the entire recording session. Subsequently, the EEG data were preprocessed using Scan 4.5 software and Curry suite 7.0 (Compumedics USA, El Paso, TX, USA). Gross artifacts were rejected by visual inspection of the recording by a trained person with no prior information on the data origin. The EEG signal analysis was performed at the sensor and at the source level, located on the scalp and the cortex, respectively.

Table 2. Drug information in patients with schizophrenia

Drug	*N*
Amisulpride	5
Alprazolam	3
Aripiprazole	6
Clozapine	1
Lithium	1
Olanzapine	13
Paliperidone	9
Quetiapine	6
Risperidone	1

Resting-state EEG paradigm

Resting EEG was recorded with eyes closed for 5 min. Data were reanalyzed using Matlab 2016 software (MathWorks, Natick, MA, USA), including a fast Fourier transform with a 1–50-Hz band-pass filter to calculate absolute power: delta (1–4 Hz), theta (4–8 Hz), low-frequency alpha (8–10 Hz), high-frequency alpha (10–12 Hz), low-frequency beta (12–18 Hz), high-frequency beta (18–30 Hz), and gamma (30–50 Hz) signals. Artifacts exceeding ±100 μV were excluded at all electrode sites. Thirty randomized artifact-free epochs (epoch length: 2.048 s) were determined for each participant.

Auditory oddball paradigm

An auditory oddball task was used in the response-contingent behavioral paradigm, comprising 240 stimuli with 2000-ms inter-stimulus intervals. Tones of 1000 Hz for standard tones (n = 200) and 1500 Hz for target tones (n = 40) were presented. The tone duration was 100 ms, with rise and fall times of 10 ms. Participants were instructed to press a button promptly in response to target tones while sitting in front of a monitor. A fixation cross was displayed in the middle of the display device. The auditory stimulus was delivered through MDRD-777 headphones (Sony, Tokyo, Japan) at 85 dB SPL in a sound-attenuated room. We used the STIM2 system

Table 1. Demographic data of schizophrenia patients and healthy controls

	Patients	Healthy controls		
Variables	Mean (SD)		Statistics	
Cases (n)	34	29		
Age (years)	41.38 (13.02)	43.38 (14.12)	t = 0.58	P = 0.562
Sex (n, male/female)	14/20	11/18	χ^2 = 0.07	P = 0.793
Positive and Negative Syndrome Scale (PANNS)				
Positive score	31.15 (5.35)	—		
Negative score	19.15 (7.44)	—	—	
General score	54.41 (9.06)			
Total score	104.71 (15.19)			

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(Compumedics USA, El Paso, TX, USA) for accurate synchronization between the stimuli and the EEG recordings. Artifacts related to eye movements or eye blinks were removed by using an established mathematical procedure.[36] Data were filtered using a 1–50-Hz bandpass filter with pre-stimulus baseline correction and were epoched from late-onset 1–500 ms. To calculate the P300 alpha frequency, a minimum epoch length above 500 ms has been recommended.[37] The absolute power was calculated using a fast Fourier transform: delta (1–4 Hz), theta (4–8 Hz), low-frequency alpha (8–10 Hz), high-frequency alpha (10–12 Hz), low-frequency beta (12–18 Hz), high-frequency beta (18–30 Hz), and gamma (30–50 Hz) signals. Artifacts exceeding ±100 μV were excluded at all electrode sites. If any remaining epoch contained significant physiological artifacts (amplitude exceeding ±100 μV) in any single cortical electrode site, it was excluded from further analysis. The participants' accuracy rate and reaction time on target stimuli differed between the two groups (accuracy – patients: 36.53 ± 7.42, HC: 39.38 ± 1.32, t = 2.20, P = 0.034; reaction time (seconds) – patients: 0.48 ± 0.16, HC: 0.36 ± 0.08, t = 3.95, P < 0.001). Only artifact-free epochs including correct- and incorrect-target stimuli were used for the analysis. The number of epochs in patients and HC was 37.82 ± 2.72 and 38.21 ± 2.50, respectively, and there was no significant difference (t = 0.58, P = 0.565). To pre-verify the difference in the P300 peak amplitude or latency between groups, P300 was evaluated on the midline electrodes (Fz, Cz, and Pz) and defined by the maximum amplitude between the 250 ms and 500 ms post-stimulus at the sensor level (epoch range: −100 to 800 ms).[38] The P300 component has been shown to be consistently generated at midline electrodes.[39–41] HC showed larger P300 peak amplitudes and shorter latencies compared with SCZ patients (amplitudes: $F_{1,\ 61}$ = 8.26, P = 0.006, η_p^2 = 0.12; latencies: $F_{1,\ 61}$ = 10.55, P = 0.002, η_p^2 = 0.15).

Source analysis

Source analyses of each band frequency for resting EEG and the P300 component were performed using the sLORETA software, which calculates a particular solution of the non-unique EEG inverse solution.[42] The sLORETA algorithm is based on the assumption that neighboring voxels tend to be activated synchronously. A three-layer realistic head model based on the Montreal Neurological Institute (MNI) 152 template provided by the Brain Imaging Center, MNI,[43] was used in the sLORETA software to solve the inverse problem. The source space in the software was restricted to the cortical gray matter and the hippocampus and was divided into a total of 6239 cubic voxels with a 5-mm resolution. The time-frequency analysis used to calculate the P300 high-frequency alpha source images was based on the mean P300 in each group, taking into account peak latency variations (1–500 ms).

Regions of interest

The region of interest (ROI) for the resting-state EEG and P300 ERP was defined in the sensor-level analysis.[44] Six regions were chosen: frontal, central, and parietal in the left and right hemispheres. Each region was averaged at three electrodes (left frontal: AF3 + F3 + F5; left central: C3 + C5 + CP3; left parietal: P5 + P7 + PO7; right frontal: AF4 + F4 + F6; right central: C4 + C6 + CP4; and right parietal: P6 + P8 + PO8). To control for effects of local specificity, the temporal regions (FT8, T8, and TP8) were excluded from the analysis, as these electrodes cover overlapping parts of the frontal, temporal, and parietal areas.

Statistical analysis

Statistical significance was set at P < 0.05 (two-tailed). Descriptive statistical analyses of the SCZ patients and HC were performed using t-tests and the χ^2-test. To examine the statistical significance of the spectral power in EEG and ERP, the resting-state EEG band power and P300 band power of the patients and HC were compared by repeated-measures analysis of variance (ANOVA). The main effect of the comparison was examined using Bonferroni corrections. At the sensor level, three within-subject factors with two measures (both hemispheres) were used, namely the frequency power values at the frontal, central, and parietal regions. The between-subject factor was the group (SCZ patients and HC). In addition, the P300 amplitude and latency were analyzed at the sensor level, with three within-subject factors with two measures (amplitude and latency), that is, Fz, Cz, and Pz, and the between-subject factor group. At the source level, the group comparison of deep source images was carried out using a statistical non-parametric mapping method (SnPM) provided with the sLORETA software. The estimated voxel activation was averaged throughout the calculated time frame and tested voxel by voxel, with independent t-tests, for the 6239 voxels, followed by adjustments for multiple comparisons (permutation: 5000 times). Repeated-measures ANOVA with Mauchly's test of sphericity and Bonferroni post-hoc tests were used for the comparison of the source activity of each group between resting-state EEG and P300 ERP. The within-subject factors were the source activity values. Slope variations of the source activity were calculated using a linear regression slope calculation. We also analyzed the symptomatic correlations between the PANSS scores and high-frequency alpha source activities using Spearman's Rho and bootstrapping repetition times of 10 000.

Results

There was no significant difference in the low-frequency alpha activity between HC and SCZ patients. The only significant difference was seen in high-frequency alpha activity. At the sensor level, the resting state high-frequency alpha activity was reduced in the right parietal region in patients (right hemisphere: $F_{1,\ 61}$ = 4.93, P = 0.030, η_p^2 = 0.080; right parietal: t = 2.05, P = 0.047; Fig. 1). There was no significant difference in the P300 high-frequency alpha activity at the sensor level (left hemisphere: $F_{1,\ 61}$ = 0.52, P = 0.475, η_p^2 = 0.008; right hemisphere: $F_{1,\ 61}$ = 1.34, P = 0.251, η_p^2 = 0.022; Fig. 1).

At the source level, the resting-state EEG high-frequency alpha source activities were reduced in the cingulate gyrus, right insula, right middle temporal gyrus, right postcentral gyrus, precuneus, right subgyral, right superior parietal lobule, right superior temporal gyrus, and right transverse temporal gyrus in SCZ patients (threshold: t = 3.74, P < 0.05; Fig. 2 and Table S1).

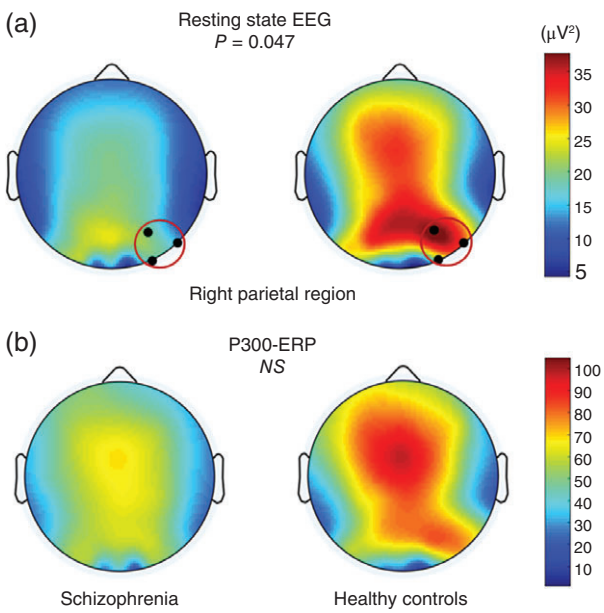

Fig.1 Reduction of high-frequency alpha activity during (a) resting-state electroencephalogram (EEG) and (b) P300 event-related potential (ERP).

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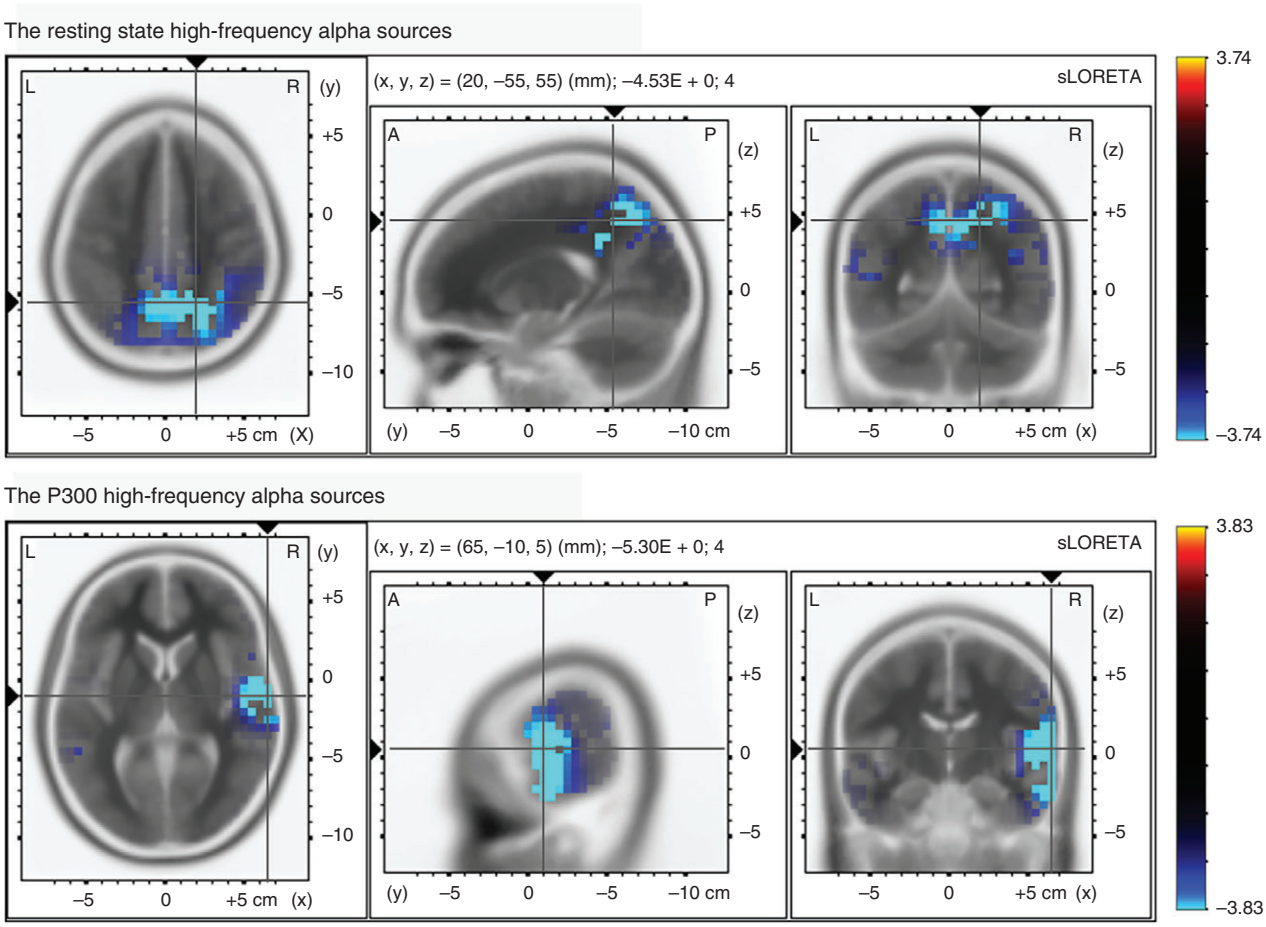

Fig.2 High-frequency alpha source deactivations in schizophrenia patients compared to healthy controls. Colored areas are deactivated source regions. The crossline indicates the minimum value of source density.

The P300 high-frequency alpha source activities were reduced in patients in the right inferior temporal gyrus, right middle temporal gyrus, right postcentral gyrus, right precentral gyrus, right superior temporal gyrus, and right transverse temporal gyrus (threshold: $t = 3.83$, $P < 0.05$; Fig. 2 and Table S2). The HC showed a decreased high-frequency alpha source activity on P300 ERP compared to resting-state EEG ($F_{7,\ 196} = 12.51$, Mauchly's test of sphericity $P < 0.001$, $\eta_p^2 = 0.309$). The decreased P300-ERP source regions in the HC were the right middle temporal gyrus ($P = 0.001$), right superior temporal gyrus ($P < 0.001$), right postcentral gyrus ($P = 0.041$), and right transverse temporal gyrus ($P < 0.001$; Fig. 3). SCZ patients displayed a significantly reduced source activity at the right postcentral gyrus ($P = 0.027$) and the right transverse temporal gyrus ($P < 0.001$; Fig. 3).

In comparison with SCZ patients, the HC showed a greater slope variation for the reduction in high-frequency alpha source activity from resting-state EEG to P300 ERP (Fig. 3). In patients, a significant negative correlation was observed between the PANSS–Positive Symptom scores and the right superior temporal gyrus source activity of the resting-state EEG ($r = -0.38$, $P = 0.029$).

Discussion

This study demonstrates significantly reduced EEG high-frequency alpha activity in SCZ patients compared to HC. Furthermore, in the current study, SCZ was associated with unsuccessful reduction of high-frequency alpha activity during the auditory P300 task compared to activity in the resting state. This result might indicate an invalid state transition in task-related neural information processing in SCZ. EEG alpha activity could contribute to a state of readiness. In resting-state and event-induced conditions, alpha activity has been shown to be involved in sensory inhibition and selection.[45] In addition, alpha activity in a psychiatric disease state may be associated with neural pathologies.[7] The value of the present results lies in the following points. First, the SCZ patients exhibited decreased high-frequency alpha activity both in the resting state and during a P300-ERP task, compared with HC. Second, HC displayed a more successful reduction of high-frequency alpha activity during the P300 task compared to SCZ patients. This result indicates that the slope variations of suppressed high-frequency alpha activity between the resting state and the P300 task were greater in HC than in SCZ patients. Third, the clinical correlation between the positive symptoms and resting-state high-frequency alpha source activity was significant in SCZ patients.

The reduced resting-state alpha activity in SCZ might be related to cognitive deficits and impaired mental abilities. A previous study reported that the alpha abnormality observed in SCZ is unique and indicates thalamic and frontal lobe dysfunction.[46] Alpha activity has been shown to decrease upon maintenance of an attentive state,[47] and reduced alpha activity is associated with error-related contexts rather than correct responses.[48] Our results suggest that altered EEG high-frequency alpha activity in the right parietal and temporal regions could be associated with the pathology of SCZ. Hinkley *et al.*[49] reported an association between the reduction of resting-state high-frequency alpha connectivity in the right temporal region and clinical symptoms of SCZ.[49] The baseline high-frequency alpha power predicted a tactile misperception of the somatosensory system.[50] In the

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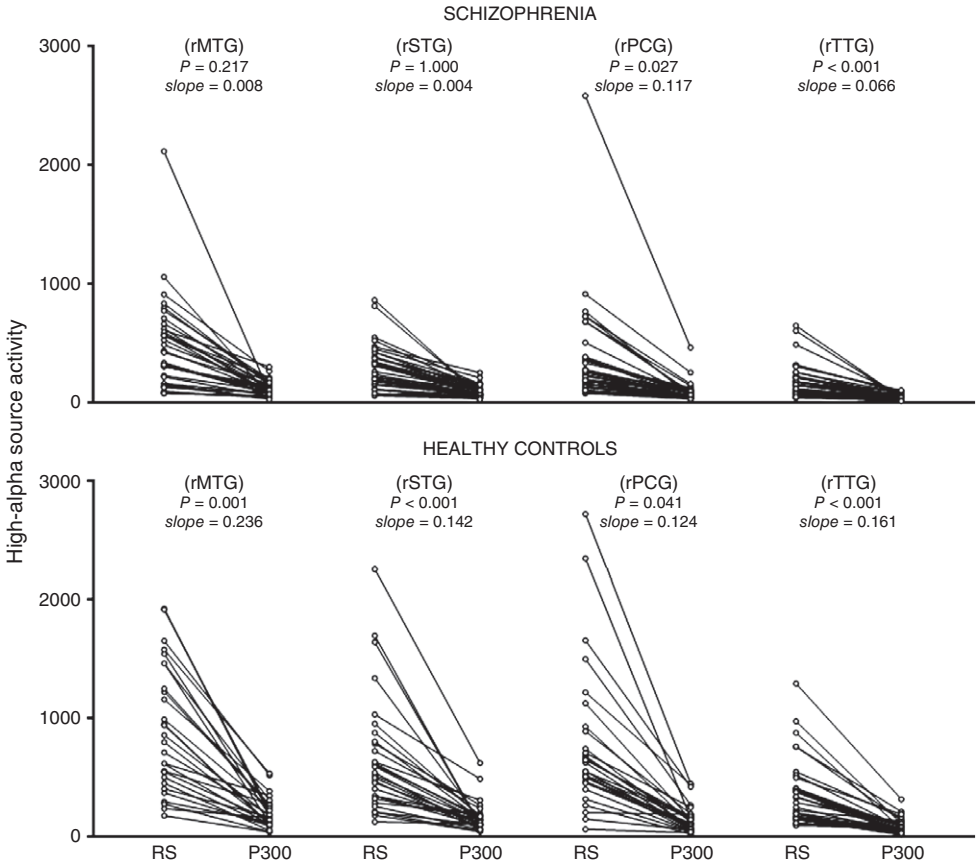

Fig.3 Deactivations in high-alpha source activity compared between RS and P300. rMTG, right middle temporal gyrus; rPCG, right postcentral gyrus; rSTG, right superior temporal gyrus; rTTG, right transverse temporal gyrus; RS, resting state.

present study, the high-frequency alpha rhythm represented a sensory blocking or modulation, and the decrease of brain activity was associated with elevated alpha rhythms. A negative correlation between alpha power and glucose metabolic rates has previously been reported in healthy participants.[51] We found differences in source level activities in the precuneus, cingulate gyrus, right superior parietal lobule, right insula, and temporal cortex. Furthermore, these areas are the key regions related to the default mode network, central executive network, salience network, and sensory motor network.[52] Even though compromised cognitive ability was not assessed by neuropsychological tests in our study, SCZ patients showed abnormal neural information processing, such as P300 deficiency during auditory input. Thus, the resting-state alpha power in the healthy participants could explain the reduced alpha power, showing an increase in brain functionality. However, suppressed alpha activity in SCZ patients was associated with brain dysfunction. Compared with HC, the patients showed decreased resting-state alpha activity and more negative symptoms as the alpha activity decreased further.[46] It has been demonstrated that high-frequency alpha activity (10–12 Hz) in parietal and occipital regions decreases in a 'seen' condition compared with an 'unseen' condition during a visuospatial task.[53] Compromised discourse processing in SCZ patients in a global context is indexed by relatively greater alpha power (8–12 Hz).[54] In addition, abnormalities in resting state gamma and beta frequencies are known as a representative trait marker of SCZ.[55–57] Increases in theta and delta frequencies and reduced beta and gamma frequencies in SCZ are consistently observed.[58] Reduced high-frequency alpha activity could stem from the fact that the bandwidth of high-frequency alpha is close to the beta and gamma frequencies.

The relationships between EEG activity and the pathology of SCZ have been previously established. An earlier study found that the reduced alpha activity in the auditory P300 paradigm results from cognitive dysfunction, which is related to event-related alpha attenuation.[59] The present study revealed a deficit in the high-frequency alpha source activity of the P300 component in SCZ patients, which may be related to symptomatic changes due to dysfunctional somatosensory processing. Event-related alpha attenuation is a trait of vulnerable homeostasis in SCZ.[59] Our results show that cognitive function in SCZ can be indicated by event-related alpha activity.

The present study demonstrates suppressed high-frequency alpha activity, compared to resting state, during a P300 task. ERD has been defined as reflecting neural function from adaptive changes of cognitive processing.[60] Mechanisms underlying human cognitive functions have been studied through induced brain state-changes using the oddball task.[12,61] Upper alpha activity would show more complexity during voluntary attention states and cognitive inhibition[62] involving working memory.[63] High-frequency pre-stimulus alpha directly modulates positive potentials, such as P1, P2, and P3, for go/no-go responses.[62] In the resting state and during cognitive task performance, the human brain detects external changes and adapts to altered circumstances, and the alpha activity corresponds to the preparatory inhibition of an event.[64] Pfurtscheller[65] suggested that the alpha activity is blocked in the time-lock domain when stimuli are presented. However, changes in alpha activity in each trial can be influenced by the inter-stimulus interval.[65] This interference effect is controlled by the baseline state that can be reflected by the resting state in eye-closed conditions.[11] According to changes in mental state, the human brain discriminates between favorable and unfavorable stimuli during an event, which is associated with EEG desynchronization. The bottom-up processing that occurs in EEG desynchronization requires a reduction in the frequency activity during sensory processing.[65,66] Alpha activity might be associated with sensory integration and with blocking by modulation of the neuronal excitatory or inhibitory activity. This is evidenced by the effect of NMDA receptor blockade on alpha activity in humans.[67] The hypofunction of the NMDA receptors in SCZ is known as cortical hyper-excitation by disinhibitory pyramidal neurons.[68] Improved cognitive performance is indexed by increased upper alpha power (individual alpha frequency, 8–10 Hz

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[±2 Hz]) at the pre-stimulus interval in humans.[69] The alpha rhythm modulates a task-dependent state with a sensory stimulus,[70] which can be interpreted as an assembly of neural populations according to task performance. Furthermore, failure to reduce alpha activity during cognitive tasks in SCZ patients could result in compromised behavioral reactions, that is, disengagement of the attentional network.[71] The present study demonstrates a functional reduction in the high-frequency alpha activity in HC, whereas SCZ patients exhibited smaller differences in slope variation in high-frequency alpha activity. This slope variation may be caused by the fact that SCZ patients compared to HC had a low level of high-frequency alpha activity in both resting and task-related conditions. The differences in slope variation in SCZ could indicate a dysfunction in sensory processing to differentiate between relevant and unnecessary stimuli. Interestingly, a real-world study found a link between neural activity and socioeconomic status, with lower socioeconomic status correlating with increased neural activity in the dorsomedial prefrontal cortex.[72] The socioeconomic status of SCZ patients may thus be closely related to unsuccessful reduction of alpha activity. Therefore, the current findings imply that the unsuccessful reduction of high-frequency alpha activity can be a hallmark of SCZ, in that alterations of neural oscillations in several conditions can be clinically qualified. Further studies will be needed to assess the slope variations of alpha activity as a potential biomarker of SCZ.

The present study demonstrates that positive symptoms were inversely correlated with resting-state EEG high-frequency alpha source activity, which is consistent with findings by Knyazeva *et al*.[5] according to whom alpha activity is inversely correlated with positive symptoms.[5] The authors therefore suggested EEG alpha activity as a clinical marker. Excessive alpha activity during auditory hallucination in the right temporal region predicted symptom severity in SCZ,[73] whereas depressed alpha activity in the parieto-occipital region reflected dysfunctional top-down processing in SCZ patients compared with HC.[74] Decreased high-frequency alpha and increased low-frequency alpha differentiated subgroups of positive and negative symptoms, respectively.[75] Temporal regions may be charged with processing auditory information and multisensory contents, and abnormalities are associated with positive symptoms. In addition, divisions of the low and high alpha bands in spectral analysis may have specific indications. For example, decreased lower alpha (8–10 Hz) and upper alpha (10–13 HZ) event-related synchronization indicate the disinhibition of cortical neurons.[76] In contrast, increased upper alpha activity (10–12 Hz) in cognitive therapy is associated with creativity,[77] while creative thinking to generate ideas is associated with an increase of high-frequency alpha activity in temporal and posterior parietal regions.[78–80] Therefore, changes in high-frequency alpha activity could indicate creativity and reflect possible effects of aberrant non-rationale symptoms, such as hallucinations and delusions.

The present study has several limitations. First, there was a dearth of information about the chronicity of illnesses and formal education levels of the patients, which makes the generalization of our findings problematic. Additionally, antipsychotics could have had an effect on the low-frequency alpha and higher gamma network.[81] Dominance of theta and delta activity during olanzapine use was observed in a previous study.[82] Because patients in the present study were administered several antipsychotics, confounding pharmacological effects might have affected the results; the effects of specific drugs are, however, difficult to estimate. Second, the sample size was relatively small. Third, the findings are limited to a group of SCZ patients and may thus not be representative of other conditions. In addition, the sLORETA software has low spatial resolution, which might lead to imprecise source density estimation. Future research should explore other patient populations with mental illnesses, such as bipolar and depressive disorders. The role of the reduction of alpha activity in SCZ also needs to be further clarified.

In summary, the impaired high-frequency alpha activity found in both a resting-state condition and a P300 task could reflect dysfunctional neural information processing in SCZ patients. Unsuccessful reduction of high-frequency alpha activity could be related to endogenous traits of SCZ. High-frequency alpha activity in resting-state EEG is directly associated with positive symptoms of SCZ. Accordingly, high-frequency alpha activity on resting-state EEG and P300 ERP can be an integrative biomarker indexing the symptomatic features, mental state, and cognitive impairments associated with SCZ.

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Disclosure statement

The authors declare no conflicts of interest.

Author contributions

K.-I.J. was responsible for the study design, data acquisition, analysis, and completion of the manuscript. J.O., W.J., and S.-H. L. contributed to the data interpretation and drafting of the manuscript. S.K., S. M.L., and S.H. were involved in the data acquisition and analysis. J.-H.C. contributed to the study design, completion of the manuscript, and supervision of the report.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1 Regions of resting state high-alpha source deactivation.

Table S2 Regions of P300 high-alpha source deactivation.

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