•ORIGINAL RESEARCH ARTICLE•

Defects of Gamma Oscillations in Auditory Steady-State Evoked Potential of Schizophrenia

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Background: Patients with schizophrenia have many cognitive deficits. Gamma oscillations exist in the human brain and are closely related to neurocognition. Auditory Steady-State Responses (ASSRs) is an electroneurophysiological index that could reflect gamma oscillations. It was found that the energy evoked by 40 Hz ASSRs in schizophrenic patients was significantly lower than that in healthy subjects. However, the correlation between ASSRs phase index and clinical symptoms and neurocognitive deficits has yet to be systematically studied. The purpose of this study was to investigate the dysfunction of neural activity of gamma rhythmdys function and its association with clinical symptoms and neurocognition in patients with schizophrenia.

Aims: To compare and verify the difference in energy and phase coherence of 20 Hz and 40 Hz ASSRs between schizophrenia and healthy participants, and to explore the correlation between schizophrenia ASSRs and neurocognitive deficits.

Method: Auditory steady-state evoked potentials by repeated auditory stimuli in 24 patients with schizophrenia and 30 healthy controls were recorded. The Positive and Negative Syndrome Scale (PANSS) was used to assess the clinical symptoms of the patients. MATRICS Consensus Cognitive Battery (MCCB) was used for the assessment of neurocognitive function. The correlation between indices, such as ASSRs energy, phase locking factor and phase coherence, and clinical and cognitive assessment was also systematically compared between two groups.

Results: Compared with the control group, the patient group had differences in cognitive domains including information processing speed (t=-2.39, p=0.021), attention/vigilance (t=-2.36, p=0.023), verbal learning (t=-3.11, p=0.003), and reasoning and problem solving (t=-2.60, p=0.012). The energy of 40 Hz ASSRs in the patient group was significantly lower than that in the control group (t=-2.291, p=0.032), and their phase locking factor and inter-trial phase coherence index were lower than control group (t=-3.017, p=0.004 and t=3.131, p=0.003), which was also significantly correlated to reasoning and problem solving function deficits.

Conclusion: Patients with schizophrenia had defects in multiple cognitive domains, and their 40 Hz ASSRs energy was low. Specifically, their phase locking characteristics and phase coherence were poor, which was to some extent related to reasoning ability and thinking disorder.

Key words: schizophrenia, auditory steady-state response, neurocognition, Gamma oscillation

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1. Background

Many cognitive deficits exist in schizophrenia. Recent studies have suggested that neural circuit abnormalities play a key role in affecting the functional connectivity [1-2] among various brain regions. The Timing mechanism in neural activity is the main mechanism for information integration and coordination among brain regions. It is achieved through neural oscillation activities, among which the 30~80 Hz neural activities (gamma oscillation) has attracted much attention. Gamma oscillations exist in the human brain[3], are involved in a variety of neurocognitive activities[4-5], and can be extracted from EEG signals. Hence, abnormal gamma oscillation in EEG can reflect the cognitive impairment of the brain.

Auditory Steady-State Responses(ASSRs) is an electroneurophysiological index reflecting neural oscillations, which may be used to measure the integrity of cortical neural oscillations.[6] ASSRs may generate responses corresponding to specific frequencies, when triggered by repeated auditory stimuli. This experimental paradigm is relatively simple, and electroneurophysiological index has good robustness. It is of important value in the evaluation of brain function in schizophrenia. A previous study found that ASSRs induced energy in the gamma band was significantly lower in schizophrenia patients than in healthy subjects.[7] A follow-up study suggested that it might be linked with volume changes in GABAergic interneurons and pyramidal cells[8], leading to excitation and inhibition deficits. Some researchers further pointed out that the ASSRs deficits might be an important cause for the abnormal sensation and perception in schizophrenia patients, which in turn hinders the subsequent information encoding and cognitive processing.[9]

Although a large number of studies have confirmed the differences in multiple frequency bands of ASSRs energy between schizophrenia patients and healthy controls[6], the correlation between abnormalities of ASSRs indices, clinical symptoms, and neurocognitive deficits remains to be explored. Early studies on steady-state response commonly paid attention to its relationship with sensory gating, hallucination and other sensory and perceptive abnormalities.[10] Subsequently, researchers found that prefrontal gamma band energy abnormalities were closely related to cognitive control deficits.[11] In fact, the cognitive processing abilities is not only related to the rhythmic energy of the neural oscillations, but crucial to the synchrony of neural activity. In recent years, researchers have used the indices such as phase locking factor, phase locking value as the measurement of phase synchronization of gamma oscillation[12], which provided a new perspective to fully understand the relevance between gamma oscillation and cognitive deficits in schizophrenia.

The aim of this study was to investigate the gamma oscillation energy and phase synchronization deficits in patients with schizophrenia, and to further explore its correlation with clinical symptoms and neurocognitive functions.

2. Subjects and methods

2.1 Study subjects

This study was approved by the medical ethics committee of Beijing Anding Hospital affiliated to Capital Medical University. All subjects volunteered to participate in the study, and the participants or their guardians provided written informed consent.

2.1.1 Case group

From December 2015 to February 2016, 24 cases out of 27 inpatients hospitalized in Beijing Anding Hospital affiliated to Capital Medical University were included. 3 cases were excluded due to inability to complete EEG signal collection. Inclusion criteria: 1) age 16 to 55 years old, male or female, right-handed, junior high school and above education level, 2) normal intelligence (IQ test value≥70), 3) normal hearing, without previous hearing problems (pure tone auditory threshold≤40dB), and 4) meeting diagnostic criteria for schizophrenia as per the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Exclusion criteria: 1) pregnant or lactating women, 2) severe somatic diseases, 3) extremely agitated, impulsive and uncooperative, 4) received electroconvulsive therapy in the past 6 months.

Medications in the case group: all 24 patients were treated with medication, including 7 cases with first generation antipsychotics, and 17 cases with second generation antipsychotics. Combined use of anticholinergic drugs, such as either trihexyphenidyl or scopolamine, was applied in 13 cases.

2.1.2 Control group

A total of 30 matched healthy participants from the local community were recruited by self-made advertisement. All 30 people were included in the control group. Inclusion criteria: 1) no history of mental disorders, 2) no history of nervous system diseases, 3) remaining criteria same as case group inclusion criteria 1-3. Exclusion criteria: have been using antipsychotic drugs, antidepressants or mood stabilizers in the past or present, remaining criteria same as the exclusion criteria of the case group. There was no statistically significant difference in gender ($\chi 2$=0.30, p=0.59), age (t=-0.44, p=0.66), or years of education (t=0.77, p=0.45) between the case group and the control group (Table 1).

2.2 Methods

2.2.1 Scale assessment and neurocognitive test

Assessment tools: 1) general information questionnaire, including name, gender, age, marriage status, years of education, occupation, use of alcohol, smoking, course of disease, diagnosis, somatic disease history, and medication, 2) Positive and Negative Syndrome Scale PANSS, Chinese version, reliability Cronbach's α=0.8707[13], and 3) MATRICS Consensus Cognitive Battery, MCCB, Chinese version.[14]

Table 1. Demographic, clinical and cognitive test results

Variable	Case (n=24)	Control (n=30)	t/χ^2 value	*P* value
Gender (male/female)	13/11	16/14	0.30	0.59
mean (sd) age	33.0(11.0)	34.2(10.3)	-0.44	0.66
mean (sd) years of education	14.0(2.0)	13.6(2.2)	0.77	0.45
mean (sd) duration of illness in months	108.8(110.2)	—	—	—
mean (sd) mg/day chlorpromazine dosage	514.7(246.4)	—	—	—
Clinical symptom scores (mean [sd])				
PANSS total score	87.8(8.3)	—	—	—
Positive symptom total score	20.6(6.3)	—	—	—
Negative symptom total score	23.9(6.8)	—	—	—
Normal symptom total score	42.4(5.1)	—	—	—
Cognitive assessment scores (mean [sd])				
Speed of processing	28.7(10.8)	35.3(9.5)	-2.39	**0.021**
Attention/vigilance	36.0(10.5)	42.7(10.3)	-2.36	**0.023**
Work memory	41.3(11.7)	46.0(10.2)	-1.59	0.118
Verbal learning	35.6(9.2)	42.8(7.7)	-3.11	**0.003**
Visual learning	40.9(15.8)	45.7(10.5)	-1.28	0.208
Reasoning and problem solving	34.7(7.7)	41.3(10.4)	-2.60	**0.012**
Social cognition	34.4(11.6)	34.4(10.8)	-0.01	0.996
Total score	27.2 (12.0)	35.7(10.2)	-2.80	0.007

Note: Except for gender, other data shown as $\overline{X}$ (s). Equivalent chlorpromazine dosage: using chlorpromazine as standard, calculation based on Chlorpromazine Equivalent Dosage (CED) conversion method. [30]

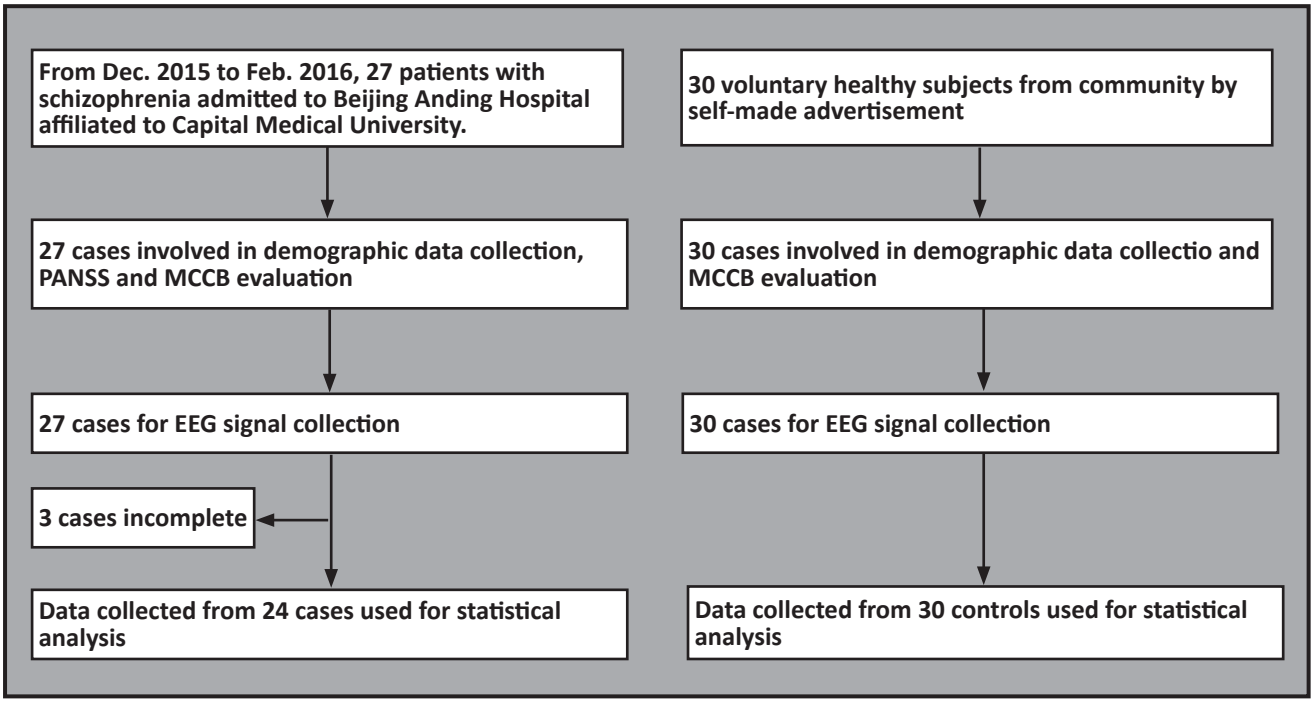
MCCB measures neurocognitive function, including: 1) speed of processing: using Trail Making Test: Part A, Symbol Coding Test, and Animal Naming Test, 2) attention/vigilance: using Continuous Performance Test-Identical Pairs, 3) working memory: Wechsler Memory Scale Third Edition, Spatial Span test and Letter-Number Span test, 4) verbal learning: using Hopkins Verbal Learning Test, 5) visual learning: using Simple Visuospatial Memory Test, 6) reasoning and problem solving: using Mazes test, and 7) social cognition: using Mayer-Salovey-Caruso Emotional Intelligence Test, Managing Emotions.

2.2.2 EEG data acquisition and processing

All subjects received EEG collection on the same day as cognitive tests. Smoking or sedative hypnotic drugs were not allowed within 8 hours before the collection. EGI (Electrical Geodesic Instrument, USA) 128-lead EEG system with saline coupling mesh electrode cap was used for EEG data collection. Signal acquisition impedance was adjusted to ≤50KΩ, with reference electrode Cz and sampling rate 1000 Hz. During the experiment, patients sat quietly in a sound and electromagnetic field shielding room. The EEG experiment was divided into 2 parts, with a 5-minute rest in between. Each part consisted of 150 trials. Each trial contained a click sound of 500 ms (80 dB white noise) followed by a quite period with an average duration of 850 ms (+-150ms). The acoustic stimuli were presented to the subjects through air conductive headphones, which repeated at a certain frequency. The repetitive frequencies of auditory stimuli in the two parts were 20 Hz and 40 Hz, respectively, and their scalp EEG data were recorded.

The EEG data were analyzed and processed using EEGLAB 13.5.4b (http://sccn.ucsd.edu/eeglab/), a neural electrophysiological analysis tool basing on Matlab and programs developed by ourselves. First, the EEG data were processed using a 0.1~90 Hz bandpass filter (finite impulse response filter). The 50 Hz power frequency noise was subject to notch processing. The reference electrode was changed to global brain average reference. Then, the whole EEG data were segmented according to the time information of the stimuli: auditory stimuli presentation time was set as

Figure 1. The flowchart of the study



0 point, and EEG data segments 200 ms before and 800 ms after the stimuli presentation onset time were kept. With regard to the single evoked response after segmentation, the main experimenter visually inspected data. Trials with EEG amplitude fluctuation greater than 200μV were considered having a large noise and removed accordingly.

Subsequently, the time-frequency distribution characteristics of each electrode EEG signal were extracted using Morlet wavelet, with the following specific steps. Continuous wavelet transformation was carried out for the segmented single EEG signal time. The EEG time range was -0.2s~0.8s (relative to the stimulus presentation time). The frequency range of wavelet transformation was 1~50 Hz. Then the temporal values of power corresponding to each frequency point were averaged across trials and thus the time-frequency distribution of the EEG power were attained channel by channel. In order to further compare the synchronization of EEG signals of each trial relative to auditory events, we used phase-locking factor (PLF)[15] and the inter-trial phase coherence (ITPC)[16] index, for the investigation of the synchrony of EEG rhythmic activities across trials. The above-mentioned rhythm and phase synchronization indices were used respectively for the investigation of the corresponding frequency band energy and phase synchronization in the EEG under 20 Hz and 40 Hz auditory stimuli, and for the comparison of their difference and relationships with cognitive processing in the two groups. In addition, the mean values of rhythmic energy and phase synchrony between 100-500 ms after stimulus presentation were used to represent the energy and phase synchrony of neural activity during auditory steady-state stimuli.

2.3 Statistical methods

Sample size calculation: according to test level α=0.05, test efficacy 1-β=0.8, ASSR-induced gamma power index reported by Hirano et al. (2015)[17], calculation yielded mean difference δ=2.595 and variation index S=2.975. Based on the two-sided test formula, the sample size required for each group was calculated to be at least 13 cases. Taking into account the rate of withdrawal, 30 cases of healthy controls and 24 cases of schizophrenia were collected.

Data were analyzed using SPSS 18. Independent samples *t*-test was used to compare the differences in EEG indices and each neurocognitive domains in auditory steady state stimuli between the two groups. Pearson correlation comparison was used for the identification of correlation among EEG indices, clinical symptoms (PANSS scores), and cognitive test battery (MCCB). Rank sum test was used for non-normal distribution data. p<0.05 was considered as statistically significant.

3. Results

3.1 Cognitive test

By comparing 7 neurocognitive functions between the case group and control group, it was found that there were statistically significant differences in speed of processing, attention/vigilance, verbal learning, reasoning and problem solving between the two groups,

and no statistically significant differences in working memory, visual learning, and social cognition (see Table 1).

3.2 Steady state response energy and phase synchronization indices

The difference in ASSRs energy between the two groups showed that there was no difference in ASSRs energy induced by 20 Hz sound stimuli, and that the ASSRs energy induced by 40 Hz sound stimuli was weaker in the case group than in the control group, with a statistically significant difference (t=-2.291, p=0.032) (see Table 2). The difference of ASSRs phase between the two groups was further analyzed, using phase locking factor (PLF) and inter-trial phase coherence (ITPC) index, respectively. The results showed that there was no difference between the two groups in the phase index of ASSRs evoked by 20 Hz sound stimuli, whereas the case group was weaker than the control group, in the two phase indexes of ASSRs evoked by 40 Hz sound stimuli , there was a statistically significant difference (PLF: t=-3.017, p=0.004; ITPC: t=-3.131, p=0.003) (see Table 2). This suggests that the synchrony of neural activity in schizophrenic patients was relatively poor.

Figure 2 and Figure 3 showed the time-frequency distribution characteristics of ASSRs under 20 Hz and 40 Hz stimulation. In the central area of the scalp, 40 Hz steady-state stimuli could elicit sustained gamma oscillation of a higher energy. In this frequency band, there was a significant difference between the schizophrenia group and the healthy control group. The time frequency distribution of phase-locked factor relationships between the two groups was similar.

3.3 Correlation between ASSRs indices and clinical and cognitive scores in case group

In the case group, there was no significant correlation between ASSRs energy and age, drug dosage, clinical symptom score, and cognitive domains. The results of the phase-locked factor were positively correlated with the scores of reasoning and problem solving in cognitive assessment (correlation coefficient = 0.55). Similar results were also verified by inter-trial phase coherence index (correlation coefficient = 0.54). This suggests that the phase coherence and stability of neural activity in schizophrenic patients were indeed defective (see Table 3). It was noteworthy that the results of the phase-locked factor were negatively correlated with the thought disorder scores in the clinical assessment (correlation coefficient = -0.41), i.e., the better the degree of phase locking in neural activity, the worse the mental disorders.

In the healthy control group the ASSRs were not correlated with age and years of education. In the case group both the 40 Hz PLF and ITPC indices were significantly associated with the reasoning and problem solving scores (correlation coefficients 0.66 and 0.69, see Table 4). This suggests that the phase synchronization of neural oscillation is a general indicator of logical reasoning and problem solving ability, and has good correlation between schizophrenia and healthy controls. In addition, the 40 Hz PLF and ITPC indices for the healthy controls were also significantly associated with "information processing speed" (correlation coefficient 0.56 and 0.62) and "total score" (correlation coefficient 0.48 and 0.59), and similar results were not observed in the case group.

4. Discussion

4.1 Main findings

4.1.1 Relationship between ASSRs power abnormality and neural oscillations in schizophrenia

A large number of studies supported that gamma oscillations were closely related to the gamma rhythm in EEG. The synaptic inhibition in the excitatory-inhibitory loop of the cerebral network is the physiological basis for the generation of gamma oscillations.[18] GABAergic (Gamma-aminobutyric acid, GABA) interneurons, under the regulation of GABAA receptor and N-methyl-D-aspartate (NMDA) receptor, release inhibitory neurotransmitters,[19] produce inhibitory postsynaptic potential, transfer inhibitory signals to glutamatergic pyramidal cells. By the amplification mechanism of the GABAergic interneurons-pyramidal cells link,

Table 2. Comparison of ASSR energy between case group and control group

Steady state response index		Case (n=24)	Control (n=30)	*t* value	*P* value	*d* value
Rhythmic energy	20 Hz	0.332 (0.271)	0.330 (0.314)	0.019	0.985	0.007
	40 Hz [a]	0.179 (0.400)	1.380 (2.431)	-2.291	0.032 *	0.655
Phase locking factor	20 Hz	0.344 (0.167)	0.378 (0.176)	-0.676	0.502	0.198
	40 Hz	0.229 (0.233)	0.463 (0.292)	-3.017	0.004 *	0.875
ITPC	20 Hz	0.205 (0.149)	0.242 (0.163)	-0.800	0.428	0.236
	40 Hz [a]	0.148 (0.209)	0.404 (0.327)	-3.131	0.003 *	0.911

Note: [a] Variance was not uniform, corrected t test was used, *: *P*<0.05 ; *d* value is cohen's *d*.

Figure 2. Time-frequency distribution characteristics of ASSRs under 20 Hz and 40 Hz stimulation in case and control groups

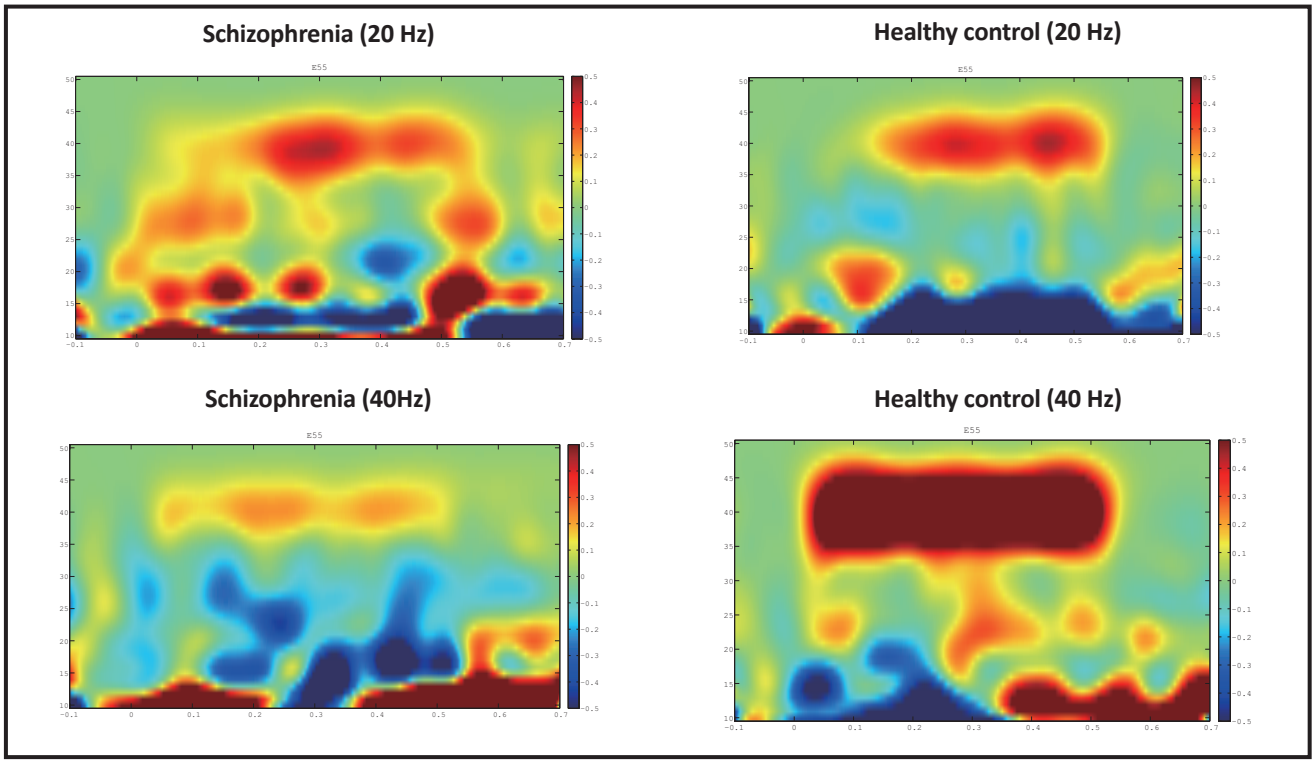
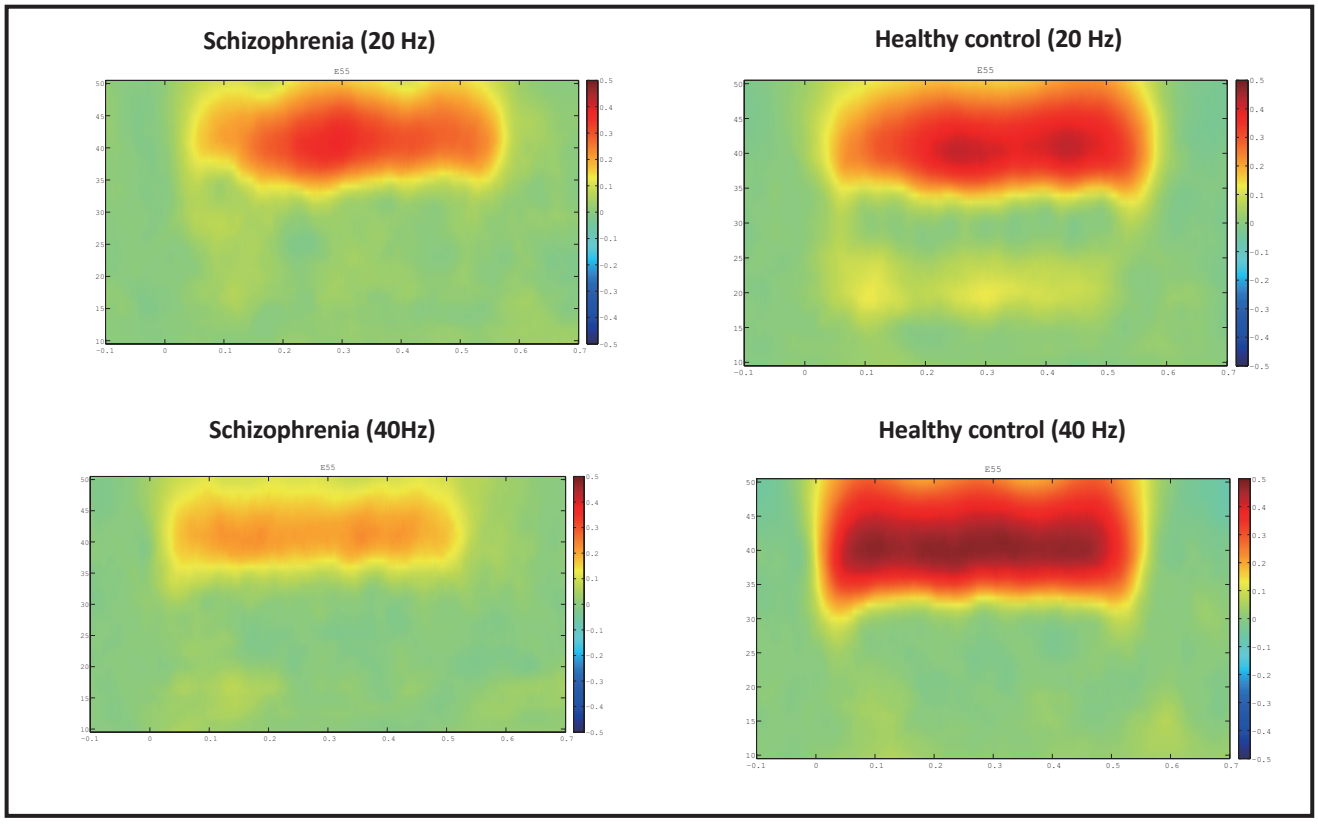


Figure 3. Time-frequency distribution characteristics of ASSRs phase locking factor under 20 Hz and 40 Hz stimulation in case and control groups



large quantities of the pyramidal cells may produce synchronized discharging activities coordinated by GABAergic interneurons synchronization activities, resulting in gamma oscillation in the brain,[20] which can be detected from the scalp EEG.

Most of the previous studies found that, compared with healthy controls, schizophrenia patients' 40 Hz ASSRs power was significantly lower, showing that their neural network had deficits in the response to steady-state auditory stimuli. A possible reason was that the GABAergic interneurons may have defects. It was also found that number of synapses of GABAergic interneurons decreased in patients with schizophrenia, and the secretion and reabsorption functions for neurotransmitter by the GABAergic interneurons were markedly weakened.[21] Therefore, the abnormality of gamma oscillation may be regarded as the results of deficits in the function of brain neural networks in schizophrenia.

This study found that the power of 40 Hz ASSRs in patients with schizophrenia was significantly lower than that of healthy controls, which was consistent with previous studies. Previous studies also found that gamma energy of patients with schizophrenia[11] was not influenced by medication, and the 40 Hz ASSRs energy of their first-degree relatives was markedly lower than healthy controls. However, no similar phenomenon was found in the patient group with schizoid personality disorder.[22] It was therefore speculated that 40Hz ASSRs energy could be a potentially stable biomarker for schizophrenia.[23]

In addition, some studies found that 40 Hz ASSRs power in schizophrenic patients was higher than in healthy controls.[24] This phenomenon might be related to the heterogeneity of schizophrenia, or to the intervention treatment for the repairing of patients' damaged neural circuit, or the initiation compensatory mechanism. Studies reported that, in some patients with schizophrenia, the baseline energy of spontaneous neural oscillation was higher than that of healthy subjects[25] before the presentation of steady-state auditory stimuli. These findings suggested that the objective markers represented by neurophysiological indices were helpful to deepen the understanding of the pathological mechanism of schizophrenia, and to further guide the categorization of diseases.

4.1.2 Deficits in synchrony of neural activity in schizophrenia

Synchronization of neural activity is also an important index to reflect the characteristics of neural oscillations. In steady-state evoked potentials, repetitive auditory stimuli continuously induce neuronal discharges, resulting in a highly synchronized neurophysiological response to stimulation. This steady-state response has the same frequency as the repetition rate of the stimulus. Therefore, there is frequency specificity in synchronization. In addition, as in each trial steady-state responses are induced by the same physical stimulation, a high degree of similarity exists between each trial. Hence, past studies used phase locking factor as an index to study the synchronization between the inter-trial steady-state evoked responses.

The results of this study showed that not only the gamma oscillations in schizophrenia were lower, but neural synchronization in schizophrenia was weaker than those in healthy controls. It suggested that there was a great difference in the inter-trial steady state response, and defects in the stability of neural circuits as well. Some studies pointed out that this synchrony defect might reflect the deteriorated neural adaptation (entrainment) to external stimuli in schizophrenia.[26] As this mechanism could be the neural basis for mechanisms such as learning and adaptation to the environment, its deficits are consistent with symptoms and cognitive deficits of schizophrenia.

It needs to be pointed out that two phase synchrony analysis methods were used in this study. The first phase locking factor was also referred to as the Inter-Trial Coherence (ITC) in the early literature. Amplitude was normalized to compare the synchronization between trials.[15] In fact, coherence usually refers to the signal synchronization between two electrodes. In this study, we need to compare the successive stability of EEG in one electrode, in order to illustrate the quality deficits in neural activity of schizophrenia, rather than the connectivity between electrodes. Hence this study also used the term "phase locking factor". The second inter-trial phase coherence (ITPC) index was essentially different from PLF. The phase information of each time point in each trial is extracted directly from the specific frequency band of EEG signals without considering amplitude. The difference between the phases at the same time point in each trials was compared to investigate the degree of synchronization. This index was put forward in recent years, frequently used for the analysis of brain magnetic signals.[16] The use of this new index in this study could provide necessary supplement to exclude the influence of amplitude, and directly examine phase abnormality of neural activity in schizophrenia.

4.1.3 The relationships between ASSRs abnormalities and clinical symptoms and cognitive deficits in schizophrenia

Cognitive processing deficit is one of the most important functional deficits in schizophrenia. It was found in this study that the case group was significantly impaired in multiple neurocognitive domains, which was consistent with previous studies.[27] Neurocognitive outcomes were influenced by factors such as medication, age, and years of education. In addition, according to literatures, the first generation antipsychotic drugs did not improve cognitive function, while the second generation antipsychotic drugs did.[28] In this study, there was no statistically significant difference between

Table 3. Correlation between 40 Hz ASSRs indices and clinical information and neural cognitive function assessment scores (n=24)

Variable Correlation coefficient EEG Index	Power	PLF	ITPC
Clinical information			
Age	0.17	-0.09	-0.10
Education years	-0.12	0.11	0.10
Duration of disease	0.24	-0.04	-0.04
Chlorpromazine equivalent dosage	-0.11	-0.07	-0.08
Positive symptom total score	-0.03	0.04	-0.07
Negative symptom total score	-0.02	-0.26	-0.23
Normal symptom total score	0.06	0.23	0.20
PANSS total score	-0.02	-0.06	-0.14
Thinking disorder 1	-0.09	0.10	0.03
Thinking disorder 2	-0.16	-0.41 *	-0.36
Cognitive function			
Speed of processing	0.01	0.18	0.28
Attention/vigilance	-0.02	-0.01	0.06
Working memory	-0.12	0.12	0.07
Verbal learning	-0.10	-0.09	-0.03
Visual learning	0.17	0.22	0.26
Reasoning and problem solving	0.32	0.55 *	0.54 *
Social cognition	0.05	0.07	0.11
Total score	0.06	0.21	0.27

Note: thinking disorder 1: composed of P2, P3, P5, P9 of PANSS scores; thinking disorder 2 composed of P2, N5, G5, G11, G13 of PANSS scores. *: *P*<0.05

the two groups in gender, age and years of education. In the case group those patients taking the first generation antipsychotics (haloperidol) combined with anticholinergic drugs (scopolamine) were having their first episode, therefore before entering this study the duration of illness was shorter and the dosage was lower. Other patients taking the second generation antipsychotics combined with anticholinergic drugs (trihexyphenidyl) also took a very small dosage. With the application of the second generation antipsychotic drug, the neurocognitive functions of the case group still had obvious deficits compared with the control group. A comprehensive analysis led to this conclusion: neurocognitive functions in patients with schizophrenia were significantly impaired, compared with healthy participants.

The results of this study showed that, regardless of whether participants were in the case group or control group the two phase synchrony measurements PLF and ITPC of ASSRs were significantly correlated with reasoning and problem solving abilities in MCCB scores, but not related to other scores, that the degree of synchrony of neural oscillations may be an important measure of reason and thought. It was worth noting that there was a significant negative correlation between PLF indices and clinical scores of mental disorders for the case group. In fact, thought form disorder is one of the most important symptoms of schizophrenia, which is closely related to logic and reasoning ability. In this study, the electroneurophysiological results showed that deficits in synchronization of neural oscillation could be the neural basis of thought disorder and

other symptoms of schizophrenia. It revealed possible association between clinical and cognitive functions, providing important enlightenment to the development of well-directed cognitive interventions.

It is noteworthy that besides the reasoning ability, the two phase synchronization indexes of 40 Hz in the healthy control group were also significantly related to the "information processing speed", and no similar results are observed in the case group. The possible reason is that the information processing speed involved in the implementation of cognitive processing and other aspects of participation, and its relationship with the neural oscillations may be affected by many factors. In the schizophrenia group there may be other factors significantly related to cognitive deficits besides neural oscillation defects.

Although there were significant differences between the schizophrenia group and healthy controls in power index of neural oscillation, there was no significant correlation between power index of neural oscillation and MCCB scores or positive and negative symptom scores in patients with schizophrenia. This suggests possible deeper deficits. From the point of view of the disease development, the clinical symptoms often occur later than the neural circuit deficits, and the stability of the neural circuit activities may demonstrate abnormality earlier than oscillation energy. Therefore, ASSRs power indices are not related to clinical scores, and are insensitive to medication, suggesting that it may reflect some quality deficits.

Gamma oscillation is also closely related to the execution of memory tasks. Gamma oscillation binds different features of the stimulus of memory objects together to form complete perception of objects. The Gamma oscillations formed by memory stimuli are involved in the memory process through two channels. First, the the gamma oscillation in higher level of the cerebral cortex modulate the responsiveness of downstream sensory neurons to stimuli, forming selective attention to enhance memory. Second, Gamma oscillations prompt neurons to synchronize their activities, resulting in the formation of synaptic plasticity, which forms traces of memory involved in short-term and long-term memory. In fact, behavioral neurocognitive measures require participants to participate in a variety of memory mechanisms. Therefore, cognitive scores in this study are more or less related to Gamma oscillation, especially in the control group. In the correlation results (Table 4), multiple indicators of ASSRs showed significant associations with multiple cognitive functions.

In addition, the selection of cognitive processing tasks also affects the correlation results. For example, there was no significant difference between the two groups in working memory items, which was not related to ASSRs power level or phase synchrony either. The possible reasons were as follows: 1) the working memory scores were affected by task difficulty and processing speed. The subjects might have adopted different strategies to complete corresponding tasks. Compensatory mechanisms also had some impact on the results. 2) The study found no difference in visual learning between the two groups, suggesting that Gamma oscillation induced by visual stimulus memory leads to complete plasticity of neurons, which compensates for the memory impairment caused by attention deficit. Therefore, short-term memory is relatively intact. Working memory Table WMS-III (Wechsler Memory Scale - Third Edition) detected mainly short-term memory. 3) After controlling speed of processing, working memory is not a unique feature of schizophrenia, while the speed of processing may be the core deficit in schizophrenia.[29] The deficiency in the above mentioned cognitive assessment tasks further illustrates the unique advantages of ASSRs as an objective biological indicator in assessment and screening for schizophrenia.

4.2 Limitations

The average duration of schizophrenia in the study group was 108 months, with large differences in the duration of disease. A sample size 24 was not enough to make detailed division according to the duration of the disease. The course of disease is one of the important factors that affect the degree of neural circuit deficits in schizophrenia. There were some limitations and deficiencies in the division of case groups and sample sizes. Although there were significant differences in the electrophysiological indices between the case group and the control group, the relationship between them and the prognosis of the disease could not be further explored. In future studies, we will include more cases, especially first episode patients and ultra-high risk populations, and carefully classify the patients according to the course of disease, with or without medication, and the types of antipsychotic drugs taken.

4.3 Implications

In conclusion, the ASSRs indices closely related to gamma oscillations might be related to abnormal functional connectivity in the brain regions of schizophrenia, and deficits in the balance of excitation and inhibition in neural circuit. The phase synchronization of gamma oscillations could further reflect the cognitive deficits such as in logic and reasoning abilities, and was closely related to core symptoms such as thought form disorder. It was speculated that it had some specificity in disease assessment and diagnosis, and could be one of the tools for schizophrenia screening. In addition, EEG signal acquisition is relatively convenient, and easy to popularize in psychiatric hospitals. The subjects did not need to respond to auditory stimuli, nor was there a specific requirement for their attention. This study used repeated auditory materials, so the evoked EEG responses were relatively stable, and were more robust

to noises. Therefore, the effect size of this study(*d*=0.8) was higher, indicating actual application value.

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Conflict of interest statement

All authors of this study have no conflict of economic or other interest.

Ethical approval

This study had been approved by the ethics committee of Beijing Anding Hospital affiliated to Capital Medical University. The acceptance number is (2017) scientific research No. 11-201723FS-2. All participants were volunteered to participate in the study, and the subjects or their guardians signed informed consent.

Authors' contributions

The author Chenhui Sun was responsible for the inclusion of subjects, electrophysiological data collection and article writing. Ping Zhou and Yu Fan were responsible for cognitive assessment. Fang Dong and Fuchun Zhou were responsible for clinical evaluation. Qing Tian was responsible for the electrophysiological data preprocessing and statistical analysis. Changming Wang was responsible for the in-depth analysis of the electrophysiological data and article writing. Chuanyue Wang was responsible for experiment design, guiding data collection, and participated in article writing.

精神分裂症听觉稳态诱发电位中 Gamma 振荡的缺陷

孙辰辉，周平，王长明，范玉，田晴，董芳，周福春，王传跃

背景：精神分裂症患者存在多种认知功能缺陷。Gamma 振荡存在人脑中，与神经认知关系密切。听觉稳态反应（Auditory Steady-State Responses, ASSRs）是一种反映 gamma 振荡的神经电生理指标，既往研究发现精神分裂症患者 40 Hz ASSRs 诱发能量较健康者明显降低，不过 ASSRs 的相位指标与临床症状及神经认知缺陷的相关性尚有待系统研究。本研究旨在深入探索精神分裂症患者 gamma 节律神经活动缺陷及其与临床症状和神经认知间的相关性。

目的：比较并验证精神分裂症与健康人群 20 Hz 和 40 Hz ASSRs 能量和相位一致性的差异，探索精神分裂症 ASSRs 与神经认知缺陷的相关性。

方法：记录 24 名精神分裂症患者和 30 名健康对照重复听觉刺激引起的听觉稳态诱发电位，采用阳性与阴性症状量表（PANSS）评估患者的临床症状，采用认知功能成套测验 - 共识版（MATRICS Consensus Cognitive Battery, MCCB）评估神经认知功能，计算 ASSRs 能量、锁相因子和相位一致性等指标与临床和认知评估的相关性。

结果：病例组在信息处理速度（*t*=-2.39, *p*=0.021）、注意 / 警觉（*t*=-2.36, *p*=0.023）、词语学习（*t*=-3.11, *p*=0.003）、推理和问题解决（*t*=-2.60, *p*=0.012）等认知领域与对照组比较存在差异，40 Hz ASSRs 能量比对照组明显降低（*t*=-2.291, *p*=0.032），锁相因子和试次间相位一致性指标均弱于健康对照（*t*=-3.017, *p*=0.004 和 *t*=3.131, *p*=0.003），且与推理和问题解决功能缺陷显著相关。

结论：精神分裂症患者在多个认知领域存在缺陷且 40 Hz ASSRs 能量偏低，特别是相位锁定特性和相位一致性较差，与推理能力和思维障碍存在一定关联。

关键词：精神分裂症；听觉稳态反应；神经认知；Gamma 振荡

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