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The Meaning of P50 Suppression : Interaction of Gamma and Alpha Waves

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Objectives Sensory gating dysfunctions in patients with schizophrenia and bipolar disorder have been investigated through two similar methods ; P50 suppression and prepulse inhibition paradigms. However, recent studies have demonstrated that the two measures are not correlated but rather constitute as distinct neural processes. Recent studies adopting spectral frequency analysis suggest that P50 suppression reflects the interaction between gamma and other frequency bands. The aim of the present study is to investigate which frequency component shows more significant interaction with gamma band.

Methods A total of 108 mood disorder patients and 36 normal subjects were included in the study. The P50 responses to conditioning and test stimuli with an intra-pair interval of 500 msec were measured in the study population. According to P50 ratio (amplitude to the test stimulus/amplitude to the conditioning stimulus), the subjects with P50 ratio less than 0.2 were defined as suppressed group (SG) ; non-suppressed group (NSG) consisted of P50 ratio more than 0.8. Thirty-five and 25 subjects were included in SG and NSG, respectively. Point-to-point correlation coefficients (PPCCs) of both groups were calculated between two time-windows : the first window (S1) was defined as the time-window of one hundred millisecond after the conditioning auditory stimulus and the second window (S2) was defined as the time-window of 100 msec after the test auditory stimulus. Spectral frequency analysis was performed to investigate which frequency band results in the difference of PPCC between SG and NSG.

Results Significant reduction of PPCC between S1 and S2 was observed in the SG (Pearson's $r = 0.24$), compared to PPCC of the NSG ($r = 0.58$, $p < 0.05$). In spectral frequency analysis, gamma band showed "phase-reset" and similar responses after the two auditory stimuli in suppressed and non-suppressed group. However in the case of alpha band, comparison showed significantly low PPCC in SG ($r = -0.14$) compared to NSG ($r = 0.36$, $p < 0.05$). This may be reflecting "phase-out" of alpha band against gamma band at approximately 50 msecs after the test stimulus in the SG.

Conclusions Our study suggests that normal P50 suppression is caused by phase-out of alpha band against gamma band after the second auditory stimulus. Thus it is demonstrated that normal sensory gating process is constituted with attenuated alpha power, superimposed on consistent gamma response. Implications of preserved gamma and decreased alpha band in sensory gating function are discussed.

Key Words P50 · PPI · Spectral frequency analysis · Gamma wave · Alpha wave.

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Introduction

P50 is an auditory evoked positive potential, which appears 40−80 msec after the onset of stimulus. This event-related potential (ERP) is used to assess information processing and sensory gating function of the central nervous system. Diminished decrement in P50 response to a second auditory stimulus has been widely reported in patients with schizophrenia[1-4] and mania[5)6)] using a conditioning-testing P50 paradigm. Such attenuation of inhibitory mechanism can be related to a sensory gating failure : an inability to filter out irrelevant noises from critical stimuli.[7)]

Along with P50 suppression paradigm, prepulse inhibition (PPI) of the auditory startle reflex is another electrophysiological index that can be used to indirectly investigate the central processing mechanism of sensory gating. It is known that a weak lead stimulus can cause an attenuated startle eye blink reflex.[8)] Reflecting P50 suppression paradigm, a failure of sensory gating, measured by reduced PPI was shown in schizophrenic patients[9-12)]

and also in bipolar disorder patients with acute psychotic mania.[13]

However, in spite of the conceptual similarities, significant correlation between these two measures (P50 suppression and PPI) could not be found in healthy subjects[14] as well as in schizophrenic patients.[15] Apparently, PPI might be a more face-valid paradigm compared to P50 suppression, because it measures motor behaviors (eye blinks) which can be observed directly and has fewer methodological concerns. Some studies reported no significant difference of P50 response between healthy subjects and those with schizophrenia.[16][17] Such a negative results were demonstrated between patients with non-psychotic bipolar disorder and normal subjects.[18] In fact, a recent meta-analysis proposed that a high heterogeneity in the results from studies on P50 suppression might account for study methodologies (e.g., sound intensity, filter setting, and participants' position).[19] Therefore, the real meaning of P50 suppression may still have been poorly understood and the inconsistent results of P50 suppression need to be elucidated.

Recently, it has been suggested that at least two roughly divided frequency bands contribute to P50 suppression phenomenon. The early gamma band response (GBR) is known to be associated with sensory registration, irrespective of stimuli or attentional status.[20] On the other hand, low-frequency responses (LFR), which occupy 1–20 Hz range, may be responsible for selective attention in stimulus processing and attenuated response was observed in patients with bipolar disorder.[21] Thus, separating P50 into specific frequency domains can allow more meticulous interpretation of P50 suppression, according to underlying cognitive mechanism.

Because of gamma band frequency (24–48 Hz), P50 wave may appear at the third peak of a gamma band after onset of stimuli. Our hypotheses in the study include : 1) P50 is composed of gamma (the third peak after stimulus) and some other slower components of electroencephalogram (EEG) activity ; 2) Gamma band would show similar responses to repeated auditory stimuli regardless of P50 suppression status, while other components would not ; 3) P50 amplitude may be decreased when these two components (gamma and other frequency bands) are at "phase-out" status, or vise-versa.

Methods

Subjects

A total of 108 patients with mood disorder (77 bipolar disorders ; 31 major depressive disorders) and 36 healthy controls from the study by Kim et al.[22] were included in the study. The patients were recruited from the outpatient clinic at the department of neuropsychiatry in Seoul National University Hospital. The diagnosis was made using the Structured Clinical Interview for Diagnostic Statistical Manual of Mental Disorder, fourth edition.

Twenty-eight patients and five normal controls were excluded because of their poor data qualities. Using a P50 amplitude ratio (P50 amplitude to test stimulus/P50 amplitude to conditioning stimulus), we divided the participants into two groups, regardless of the psychiatric diagnosis. The suppressed group (SG) was operationally defined as the subjects with P50 ratio less than 0.2 ; thirty-five participants were included in the group. The non-suppressed group (NSG) included those with P50 ratio greater than 0.8, resulting in 25 individuals allocated to the group. To see a clearer contrast, we defined both SG and NSG strictly by P50 ratio. The intermediate group was excluded from the analysis.

P50 procedure

Electroencephalographic recordings were obtained between 9 : 00 a.m. and 12 : 00 p.m. Subjects were placed in a supine position and instructed to relax but stay awake. A total of 100 pairs of conditioning and test stimuli were presented with an intra-pair interval of 500 msec and the inter-pair intervals were 6–8 sec. The clicks had duration of 1 msec and a mean auditory intensity of 90 dB. Recordings were obtained using neuroscan and digitally filtered with a 0.3–48 Hz, at a sampling rate of 1000 Hz for each trial. The trials which contained artifacts (± 50 μV potentials) were excluded during the averaging process.

Using a standardized procedure according to P50 paradigm, the averaged ERP was obtained from each subject. The P50 wave to conditioning stimulus was selected as the highest positive peak within the time-window of 40–80 msec after the presented stimulus. The test P50 was determined as the most positive deflection in the latency range, equal to the latency of the conditioning P50 response ± 10 msec. The amplitude of each wave was defined as the absolute difference between the P50 peak and the preceding negative trough. The P50 ratio was defined as already mentioned.

Statistical analysis

The correlation between conditioning and testing event-related potentials

We assumed that if electrophysiological responses in the time-window of 100 msec following the conditioning stimulus (S1) and that following the test stimulus (S2) are similar, their correlation might be high. To investigate the similarity of evoked potential (μV) over time between pre-defined time-windows, we adopted a new methodology ; the point-to-point correlation coefficients (PPCCs). The PPCCs were calculated between S1 (100 msec time-window after conditioning stimulus) and S2 (100 msec time-win-

dow after test stimulus), using Pearson's correlation tests. To identify the between-group difference, PPCCs from individual subjects were tested with independent sample t-tests. As a control interval, the same analysis was done between the two time-windows of 300−400 msec following the conditioning (S3) and test stimuli (S4), during which effects of auditory stimuli would dissipate. The statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 19.0 for Windows (SPSS Inc., Chicago, IL, USA).

Wavelet analysis

The averaged signals from each individual were split into gamma (24−48 Hz), beta (12−24 Hz), alpha (8−12 Hz), theta (3−8 Hz) and delta (1.5−3 Hz) bands by the wavelet analysis using Autosignal software (ver 1.7, Systat Software, San Jose, CA, USA). The grand-average responses for each spectrum band were calculated in the both groups, and the point-to-point trajectories of the grand-average potential were plotted two-dimensionally (abscissa ; S1, ordinate ; S2). Then, the PPCCs between S1 and S2 were calculated in all 5 bands in each individual and independent t-tests were done to find significant between-group difference.

Results

The overall grand-average responses of the suppressed group and the non-suppressed group to auditory clicks are shown in Fig. 1. Inhibited P50 response to test stimulus is clearly demonstrated in the graph of the suppressed group, while similar P50 wave patterns to both clicks are observed in the non-suppressed group.

As we have expected in the hypothesis, the PPCC between S1 and S2 in averaged potential of SG was significantly lower than that in NSG (mean 0.24 and 0.58, respectively ; $p < 0.05$)(Table 1). This effect dissipated rapidly and the correlation was barely discernible 300 msec after the stimulus (SG = 0.07 and NSG = 0.01 ; $p = 0.62$).

After spectral frequency analysis was performed, two-dimensional plots of grand-average responses in both groups at each frequency were obtained (Fig. 2). As a result, alpha and beta bands showed negative slopes between S1 and S2 in the SG, but not in the NSG.

The PPCCs of gamma band between S1 and S2 were high in both groups (SG = 0.40 and NSG = 0.52)(Table 2). The similar response of gamma wave between S1 and S2 dissipated with the elapse of time ; the correlation level dropped significantly at 300−400 msec after each stimulus (SG = 0.03 and NSG = −0.02). For alpha band, a small negative correlation was shown in SG (−0.14), while higher correlation existed in NSG (0.36). Between-group difference in correlation level of alpha was statistically significant. Different from what is expected, no significant between-group difference was found regarding correlation levels in beta band.

As shown in Fig. 3, the phase-reset of gamma band occurred after conditioning and test stimuli in both groups. For alpha band, however, phase-reset after test stimulus was absent in the SG and

Table 1. Comparison of point-to-point correlation coefficients of the averaged evoked potentials between suppressed group and non-suppressed group

Comparison interval	Correlation coefficient		p-value
	Suppressed group	Non-suppressed group	
S1 and S2	0.24	0.58	< 0.05
S3 and S4	0.07	0.01	0.62

S1 : 0−100 msec time-window after conditioning stimulus, S2 : 0−100 msec time-window after test stimulus (i.e., 500−600 msec after conditioning stimulus), S3 : 300−400 msec time-window after conditioning stimulus, S4 : 300−400 msec time-window after test stimulus (i.e., 800−900 msec after conditioning stimulus)

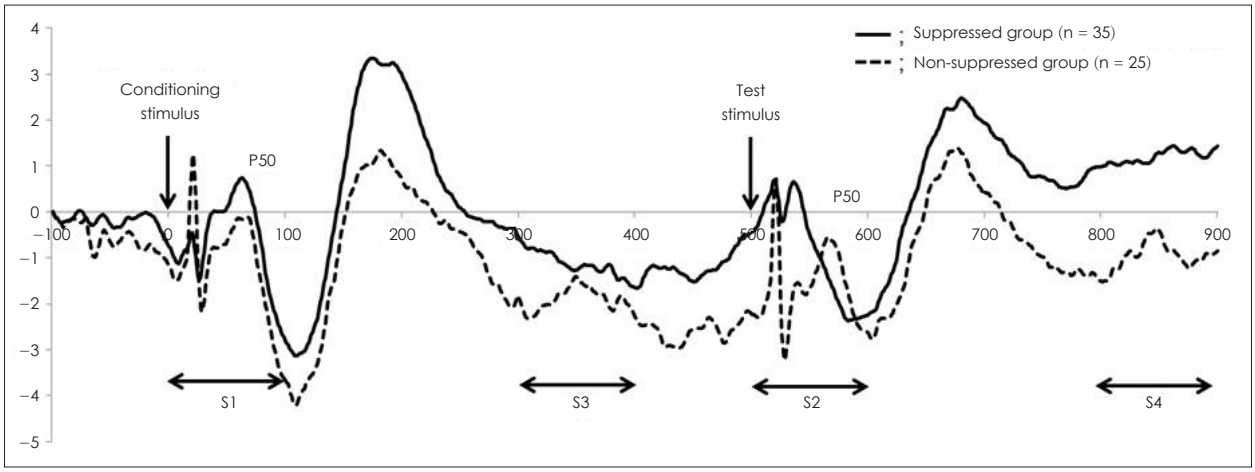

Fig. 1. Grand-average wave forms of suppressed group and non-suppressed group.

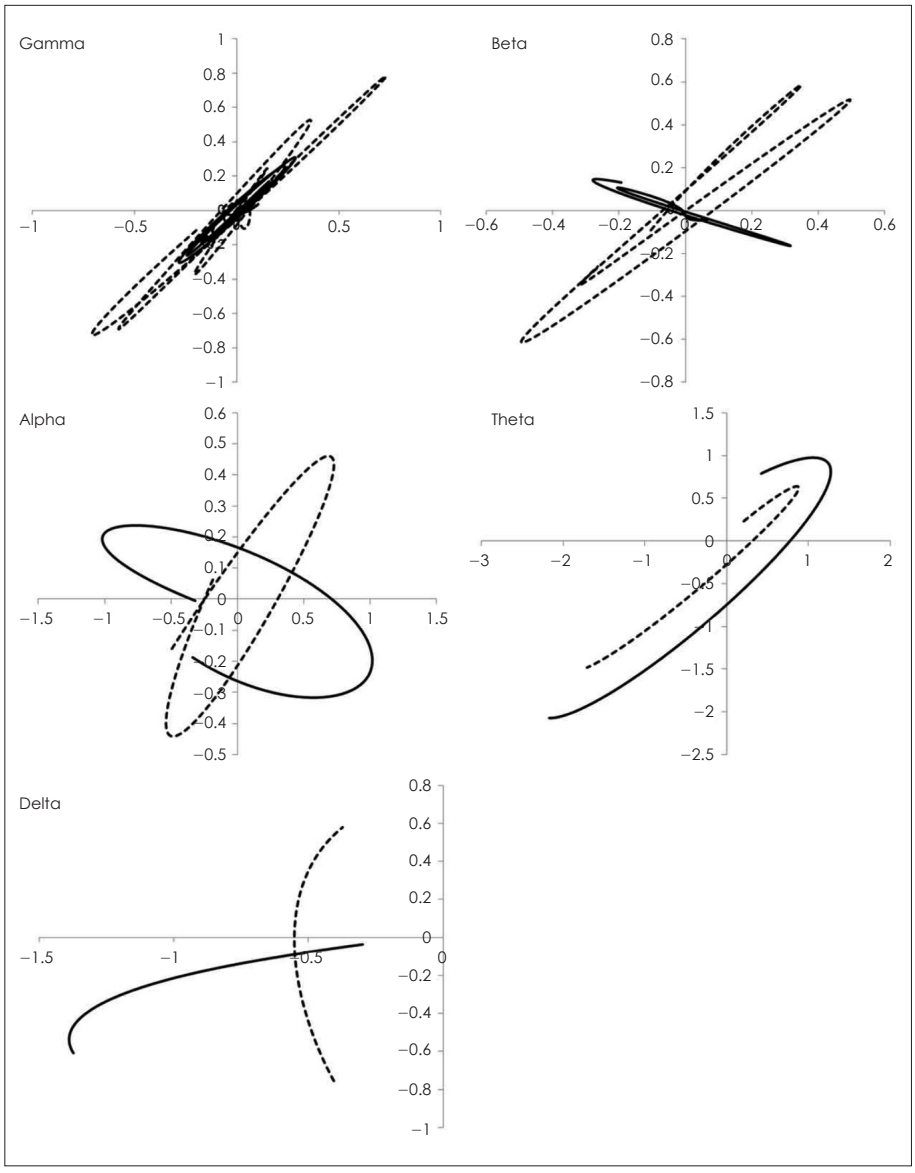

Fig. 2. Two-dimensional-plots of the trajectories of the grand-average responses in suppressed group (SG) and non-suppressed group (NSG). Solid line : SG, Dotted line : NSG, Abscissa : point-to-point trajectories from 0 to 100 msec after the conditioning stimulus, Ordinate : point-to-point trajectories from 0 to 100 msec after the test stimulus.

Table 2. Spectral frequency analysis of the averaged evoked potentials

Frequency	Correlation coefficient					
	S1 and S2		p	S3 and S4		p
	SG	NSG		SG	NSG	
Gamma (24−48 Hz)	0.40	0.52	0.24	0.03	−0.02	0.66
Beta (12−24 HZ)	0.11	0.28	0.29	−0.10	−0.14	0.79
Alpha (8−12 Hz)	−0.14	0.36	<0.05	0.17	0.06	0.43
Theta (3−8 Hz)	0.79	0.65	0.22	0.25	0.21	0.78
Delta (3−5 Hz)	0.19	0.11	0.69	0.42	0.13	0.15

Comparison of point-to-point correlation coefficient between suppressed group and non-suppressed group in each frequency band. S1 : 0−100 msec time-window after conditioning stimulus, S2 : 0−100 msec time-window after test stimulus (i.e., 500−600 msec after conditioning stimulus), S3 : 300−400 msec time-window after conditioning stimulus, S4 : 300−400 msec time-window after test stimulus (i.e., 800−900 msec after conditioning stimulus). SG : suppressed group, NSG : non-suppressed group

resulted in the desynchronization with gamma, which was reset after the stimulus. When gamma and alpha band were plotted together, we could have reconstructed P50 responses that were similar to grand average responses in two groups (Fig. 3).

Discussion

The spectral frequency analysis of grand-average response of auditory-evoked potential enabled further investigation to find the meaning of P50 suppression phenomenon. The results of the present study showed that P50 can be interpreted as an interaction between gamma and alpha waves.

The P50 suppression to auditory stimuli has been indicated as P50 ratio, which is obtained by dividing the amplitude of the second stimulus by the amplitude of the first click. However, we

hypothesized that subjects with low P50 ratio (SG) might also show low correlation level between 0−100 msec time-windows after conditioning and test stimuli compared to NSG. The PPCCs in NSG are significantly higher than the suppressed subjects which means that similar response is occurred in the non-suppressed subjects after the presentation of repeated stimuli.

As shown in Fig. 3, phase-reset of gamma band has occurred with high correlation between S1 (0−100 msec) and S2 (500−600 msec) after both auditory stimuli in both SG and NSG, while alpha was reset only in the non-suppressed subjects. Thus phase synchronization of gamma and alpha rhythm at about 50 msec after the second stimulus can leads to a deficit of P50 suppression, while desynchronization or phase-out of alpha with gamma band can results of suppressed P50 response which has been considered as a representative index of normal sensory gating function.

Previous studies adopting the spectral frequency analysis divided grand-average response of EEG into the gamma band response (20−50 Hz) and low frequency response (1−20 Hz).[20)21)] GBR showed no significant group (schizophrenia or bipolar disorder, control) × click interaction in the studies. However, phase-reset and similar wave pattern after both stimuli was observed re-

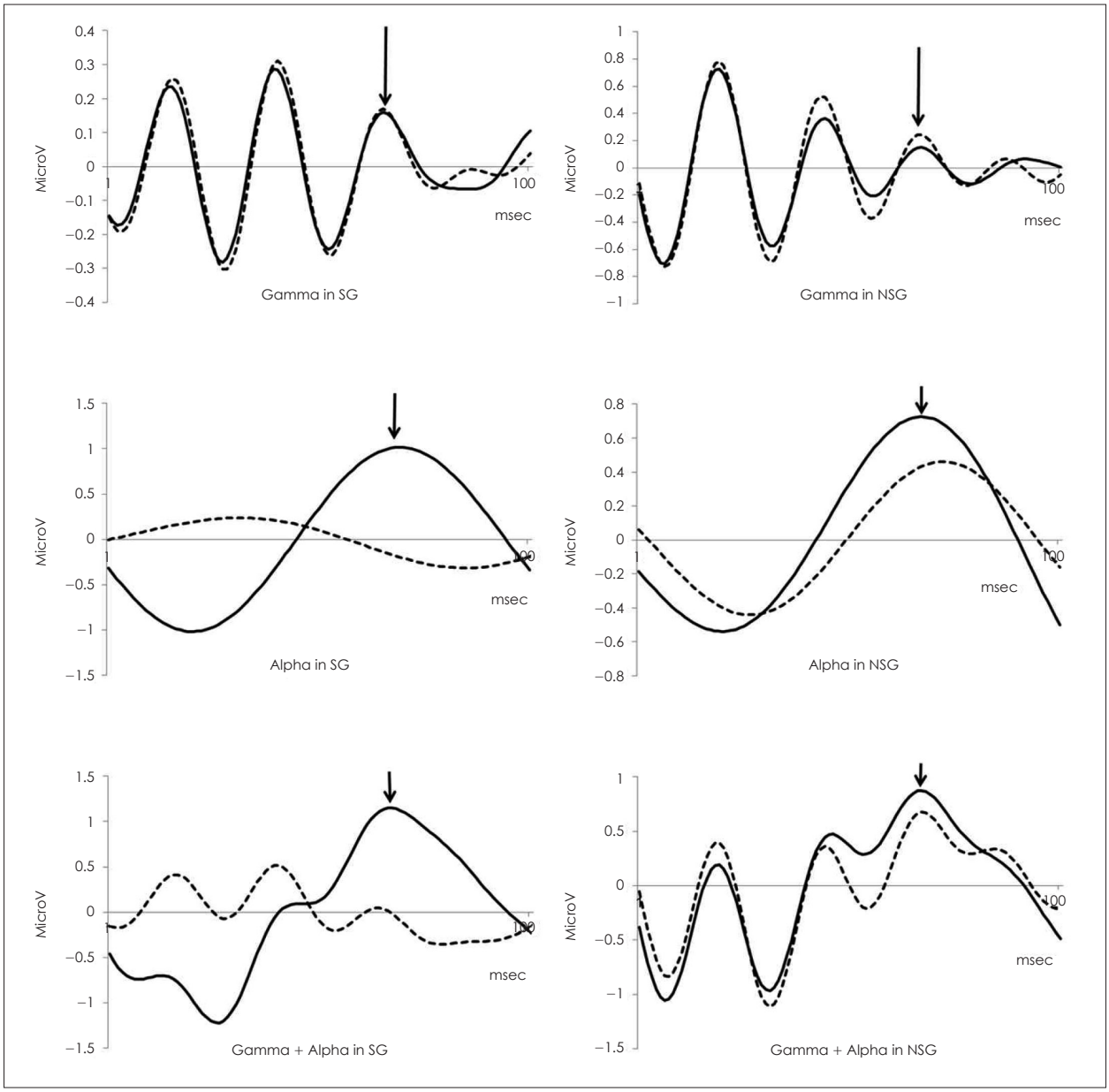

Fig. 3. Grand-averaged wave forms of gamma, alpha and superimposed gamma and alpha frequency (G + A). The left columns denote the suppressed group (SG) and the right columns denote the non-suppressed group (NSG). Solid line : wave form of 0−100 msec time-window after conditioning stimulus, Dotted line : wave form of 0−100 msec time-window after test stimulus. ↓ : P50 responses.

peatedly in GBR in patients and normal subjects. In our study, irrespective of psychiatric diagnosis, the correlations of gamma response after 0−100 msec of auditory stimuli of 500 msec interstimulus interval were high in NSG and also in SG. The gamma wave is known to have a specific function of brain. The gamma oscillation has been considered as a regular temporal reference signal of brain activity, the 'clock'.[23] Low amplitude responses to steady-state stimuli in schizophrenia were reported, and that phenomenon means the defect of neural synchronization and sensory processing.[24)25)] In another study, the same gamma ERP was reported in 0−150 msec after auditory stimuli regardless of auditory experimental paradigms. Thus it has been indicated that the gamma activity is highly responsive to external stimuli and may represent early sensory processing or registration.[20)] In the present study, high correlation of gamma band to repeated stimuli in both groups speculated the hypothetical gamma band function.

The alpha band, which is called posterior dominant rhythm shows the highest activity in subjects with 'idling state'. The regions of occipital, parietal cortex and thalamus are known to be involved in alpha generation. But the functional role of alpha rhythm is still unclear. By using ERP paradigm, it is demonstrated that alpha is related to visuospatial attention in human[26)] and phase-reset or synchronization in the alpha is responsible for effective activation of neurons.[27)] Previously, theta band in LFR was associated with new information encoding and memory function.[28)] However, change in alpha band has not been highlighted in spectral frequency analysis studies. In our study, phase-reset of alpha band occurred by an external stimulus, such as the first or conditioning auditory stimulus and it was not reset after the second or test stimulus given shortly after the first stimulus, in normal suppressed condition. The effect of test stimulus is filtered out in this case. However in the non-suppressed subjects, it was not filtered and similar alpha response to conditioning and test stimuli were presented. Thus, it is suggested that the gating problem expressed by inhibited P50 suppression is related to change in alpha activity to test stimulus. Contrary to previous concepts, it is suggested that ability of selective attention to external stimuli might be more important than pre-attentive process in P50 suppression phenomenon.

Limitations of the present study include that patients with mood disorder and normal subjects were not separated. Because P50 suppression in patients with mood disorder was known to be state-dependent, and euthymic patients in our study also showed normal sensory gating function in a previous study, we have divided subjects into two groups by P50 ratio regardless of psychiatric diagnosis. In terms of a sensitivity analysis, we further investigated the PPCCs exclusively in patients with mood disorder, excluding normal subjects from SG and NSG. Accordingly, thirteen participants were excluded (10 in SG and 3 in NSG) from the initial study sample. However similar PPCCs were obtained. However, disorder or medication effects cannot be fully excluded from the P50 suppression pattern shown in our results.

The present study has revealed that conventional conceptualization of P50 suppression in explaining sensory gating phenomenon has to be reconsidered as an interaction of distinctive cognitive domain. In future studies, the investigation of neuropsychological correlates, such as selective attention, is needed, especially in patients with schizophrenia or mood disorder.

Conflicts of interest

The authors have no financial conflicts of interest.

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