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P300 amplitude over temporal regions in schizophrenia

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Abstract To examine the left temporal scalp area reductions of P300 amplitude, event-related potentials (ERPs) during a standard oddball task were recorded in 57 schizophrenic patients and 33 normal controls. The P300 amplitude at T3 was not significantly smaller than that at T4 in schizophrenic patients. In the ANOVA analysis of the P300 peak amplitude and PCA factor scores, significant lateral topographical differences in P300 were not present between patients and controls. However, in schizophrenia, patients in the low T3 P300 group were older and consuming higher doses of antipsychotic medicine than those in the high T3 P300 group, and they had relatively low P300 amplitudes and significantly delayed P300 latency, compared with those in the high T3 P300 group. These findings suggested that although the reduction in the left temporal P300 amplitude did not necessarily exist in schizophrenic patients, it may be associated with the severity of the disease process and/or impairment of cognitive function.

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Introduction

Event-related potentials (ERPs) are objective indices of human information processing, and provide a reliable method for evaluating the impairment of information processing in patients with mental disorders (Coull et al. 1988, Frodl-Bauch 1999, O'Donnell et al. 1999). Many ERP studies in schizophrenia have focused on the abnormalities in the P300 component, which is an endogenous positive potential that occurs with an approximate latency of 300 ms after the presentation of task-relevant or novel stimuli embedded among irrelevant stimuli (Donchin, 1988). Most previous studies have demonstrated the reduction in the P300 amplitude and the delay of the P300 latency in schizophrenic patients, compared with those of normal controls (Prichard 1986, Ford 1999). The reduction in the P300 amplitude is one of the most replicated biological findings in schizophrenic patients. Moreover, some studies have noted smaller P300 amplitudes over the left rather than the right temporal region in schizophrenia. This asymmetry of the P300 amplitude was suggested to be associated with left hemisphere structural abnormalities (McCarley et al. 1989, 1993). Moreover, this left-sided P300 abnormality was present in first-episode schizophrenia (Salisbury et al. 1998), which suggested that left temporal lobe dysfunction is present at the onset of schizophrenia.

However, other studies could not fully replicate these findings. Pfefferbaum et al. (1989) recorded auditory and visual ERPs in schizophrenic patients and normal controls, and found no lateral differences between patients and controls. Havermans et al. (1999) investigated MRI-defined volumes of temporal lobe structures and P300 amplitude in schizophrenic patients and controls. Although they found left P300 amplitude reduction in schizophrenic patients compared with that in controls,

there was no evidence of volume reductions in the temporal lobe in schizophrenia and correlations between volumes of the left temporal lobe structures and left-sided P300 amplitudes were not significant.

In the present study, to examine this inconsistency, we investigated whether the finding of the left-sided P300 abnormalities in schizophrenia was replicated using substantial numbers of patients.

Methods

Subjects

The study sample consisted of 57 physically healthy subjects (26 males and 31 females) who gave written informed consent before participating in this study. They were outpatients at the Department of Psychiatry, Showa University Hospital and Tokyo University Hospital. The patients were diagnosed as schizophrenia according to the DSM-IV (APA 1994) on the basis of a structured psychiatric interview, the Schedule for Affective Disorders and Schizophrenia (Spitzer and Endicott 1978), and medical records. None of the subjects had a history of electroconvulsive shock treatment, alcohol or other drug abuse and dependence, or a neurological illness affecting the central nervous system. Their mean age was 30.1 years (SD 10.1), the mean age at onset 22.7 years (SD 6.7), the mean duration of illness 7.4 years (SD 8.2), and the mean duration of education 13.3 years (SD 3.4). All subjects, except one, were treated with neuroleptics, and their mean daily dosage of chlorpromazine equivalent was 561.1 mg (SD 561.7). The mean total score of Brief Psychiatric Rating Scale (Overall and Gorham 1962) on the day of testing was 34.3 (SD 8.4), which indicated that the symptoms of the patients were mild. Thirty-three normal volunteers (15 males and 18 females, mean age 27.8 years, SD 5.8) served as the control group. The normal subjects were recruited from the hospital staff and students of Tokyo University and Showa University Hospital. All patients and normal controls were right-handed according to the Edinburgh Inventory of Handedness (Oldfield 1971). This study was approved by the Ethical Committee of the University of Tokyo.

ERP recordings

Event-related potentials were recorded during an auditory oddball task in a soundproof room. Subjects were presented with a series of 270 auditory stimuli with a fixed interstimulus interval of 1500 ms. In this task, 85 % of the stimuli were tones of 1 kHz, and the other 15 % tones of 2 kHz. Stimuli were presented in a Bernoulli sequence. The stimulus intensity was 75 dBSPL, and the tone duration 50 ms, with a rise/fall time of 10 ms. The subjects were instructed to press a button as quickly as possible for the infrequent high-pitch tones.

According to the international 10–20 system, the scalp electroencephalogram (EEG) was recorded with Ag/Ag-Cl disc electrodes at 16 electrode sites (Fp1, Fp2, F3, Fz, F4, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, Oz) monopolarly, referred to linked earlobes. The bandpass was set at 0.15–120 Hz. Vertical and horizontal electrooculograms (EOG) were recorded from electrodes placed below and at the outer canthus of the right eye. EEG samples were acquired every 2.5 ms from 40 ms before to 600 ms after the stimulus onset. Trials contaminated by peak to peak potentials of grater than 100 μV or accompanied by EOG of grater than 75 μV were eliminated from the averaging. The responses to frequent and rare tones with correct reactions were averaged separately. P300 was defined as the most positive peak between 250 and 500 ms poststimulus. Amplitudes were measured with respect to an average voltage during the 40 ms prestimulus. The P300 amplitude and latency for target stimuli at 5 electrode sites (Fz, Cz, Pz, T3, and T4) were analyzed.

Principal component analysis

In addition to the baseline to peak measurement, principal component analysis (PCA) was performed to obtain ERP measures in which component overlap had presumably been reduced. The original waveforms were reduced by averaging every four adjacent time points. PCA with Varimax rotation was first performed on each group's averaged ERP waveforms from 0 to 600 ms after the stimulus onset. Since separate PCAs of each group's ERPs produced highly similar factor structures, the PCA was performed across groups.

Scalp current density (SCD) mapping

The scalp potential was reconstructed by spherical spline interpolation (Perrin et al. 1989). The SCD distributions were then obtained by computing the special derivatives of the spherical spline functions used in the potential map interpolation (Nunez 1981).

Statistical analysis

In comparing patients with controls, and the high T3 group with the low T3 group, repeated measures analysis of variance (ANOVA) was performed using five measures (Fz, Cz, Pz, T3, T4), with the electrode site as a within-subjects variable and the group as a between-subjects variable (overall ANOVA), for P300 amplitude and latency, respectively. If a group effect or an interaction effect between the group and electrode site was significant in the overall ANOVA, midline (Fz, Cz, Pz) and lateral (T3, T4) ANOVAs were performed for P300 amplitude and latency, respectively. Pearson product moment coefficiencies were calculated between the ERP variables and clinical measures in the patients.

Results

Behavioral findings

Table 1 shows the mean reaction time and correct response rate of the two groups. Compared with that in controls, the mean reaction time in schizophrenic patients was significantly delayed (t-test: $t=-3.226$, $df=88$, $p < 0.01$). The mean correct response rate did not differ significantly between the two groups.

P300 amplitude and latency

Patients vs. controls

Grand mean ERP waveforms for target stimuli in the oddball task of the two groups are shown in Fig. 1. Generally, compared with that in controls, the P300 amplitude was smaller and the P300 latency was delayed in the schizophrenic patients.

Table 1 Means and standard deviations of correct response rate and reaction time of schizophrenic patients and normal controls

	Control	Schizophrenic
Correct response rate (%)	96.2 (11.3)	94.7 (9.1)
Reaction time (ms)*	331.0 (63.6)	409.9 (131.3)

* $p<0.01$

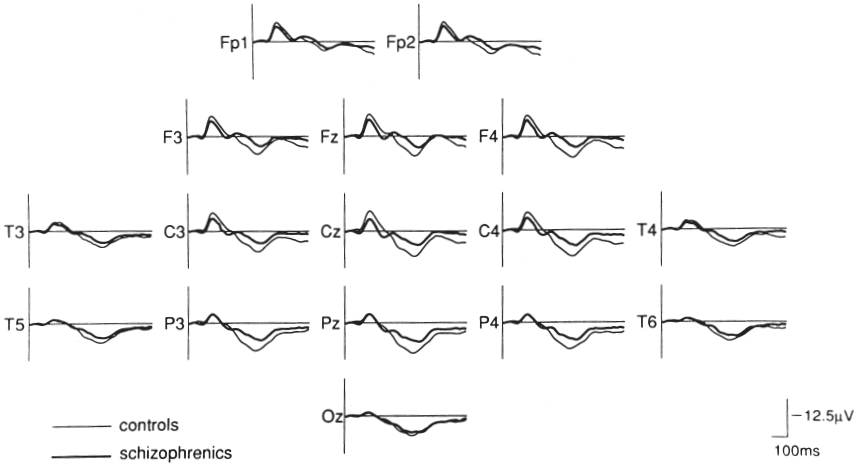

Fig. 1 Grand mean ERP waveforms for target stimuli in the oddball task of the schizophrenic patients and normal controls. Negativity is upward.

Table 2 shows the mean P300 amplitude and latency of the two groups. For the P300 amplitude, in the overall ANOVA, there was a group effect ($F[1, 88]=4.671$, $p < 0.05$) and an electrode site effect ($F[4, 88]=44.063$, $p < 0.0001$). In the midline ANOVA there was a group effect ($F[1, 88]=4.869$, $p < 0.05$) and an electrode site effect ($F[2, 88]=44.822$, $p < 0.0001$), and in the lateral ANOVA a group effect was marginally significant ($F[1, 88]=3.114$, $p < 0.1$). The interaction effect between the group and electrode site was not significant in these analyses, which indicated that the distribution of P300 did not differ between the two groups. In both groups, there was no significant difference between the P300 amplitude at T3 and T4, although the mean value of the P300 amplitude at T4 was larger than that at T3.

For the P300 latency, in the overall ANOVA, there was a group effect ($F[1, 88]=10.050$, $p < 0.01$) and an electrode site effect ($F[4, 88]=2.701$, $p < 0.05$). In the midline ANOVA there was a group effect ($F[1, 88]=10.762$, $p < 0.01$) and in the lateral ANOVA there was also a group effect ($F[1, 88]=4.838$, $p < 0.05$).

High T3 group vs low T3 group

The ratio of the P300 amplitude at T3 and at T4 (T3/T4 ratio) was calculated for each schizophrenic patient. The mean T3/T4 ratio was 0.92 (SD 0.51). Patients whose T3/T4 ratio was larger or smaller than 0.92 were defined as the "high T3 group" or the "low T3 group", respectively. Table 3 shows the clinical characteristics of the two groups. Patients in the high T3 group were younger ($t=-2.372$, $df=57$, $p < 0.05$) and were taking lower doses of antipsychotic medicine ($t=-3.025$, $df=57$, $p < 0.01$) than those in the low T3 group. Six patients in the high T3 group and 4 in the low T3 group were taking atypical antipsychotics. The remaining patients were taking typical antipsychotics. The ratio of the patients taking atypical antipsychotics was not different between the two groups (χ^2 test). In addition, the ratio of the patients who were taking antiparkinson drugs or benzodiazepines was not different between the two groups (χ^2 test).

Figures 2 and 3 show the mean P300 amplitude and latency of the two groups. For the P300 amplitude, in the overall ANOVA, there was a trend for a group effect ($F[1,88]=3.898$, $p < 0.1$), an electrode site effect ($F[4, 88]=22.325$, $p < 0.0001$), and an interaction effect between the group and electrode site ($F[4,88]=6.961$, $p < 0.0001$). In the midline ANOVA there was a trend for a

Table 3 Clinical characteristics of the high and low T3 groups

	High T3 group	Low T3 group
Number (male:female)	26.0 (9:17)	31.0 (15:16)
Age *	26.8 (10.0)	32.8 (9.3)
Age at onset	21.5 (5.5)	23.7 (7.4)
Duration of illness**	5.3 (1.4)	9.2 (1.5)
Education	13.0 (2.8)	13.5 (3.9)
BPRS total score	32.5 (7.2)	35.9 (9.2)
Daily dosage***	331.5 (269.8)	753.7 (666.6)
Antiparkinson drugs	21	29
Benzodiazepines	15	24

* p<0.05; ** p<0.1; *** p<0.01

Table 2 Means and standard deviations of the P300 amplitude and latency in schizophrenic patients and normal controls

P300 amplitude (μV)	Fz	Cz	Pz	T3	T4
Schizophrenics	7.2 (3.3)	9.4 (3.4)	11.0 (3.9)	6.5 (3.2)	6.9 (2.6)
Controls	5.9 (4.2)	7.6 (4.8)	8.6 (4.9)	5.3 (3.6)	5.9 (3.0)

P300 latency (ms)	Fz	Cz	Pz	T3	T4
Schizophrenics	325.3 (29.1)	316.0 (28.0)	316.2 (29.8)	329.8 (30.6)	324.1 (30.2)
Controls	340.4 (32.8)	337.2 (32.9)	341.6 (37.6)	344.9 (38.6)	339.2 (36.6)

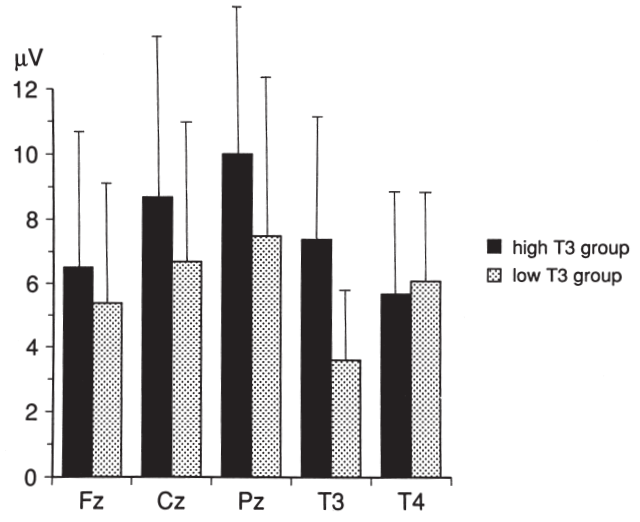

Fig. 2 Means and standard deviations of the P300 amplitude in the high and low T3 groups.

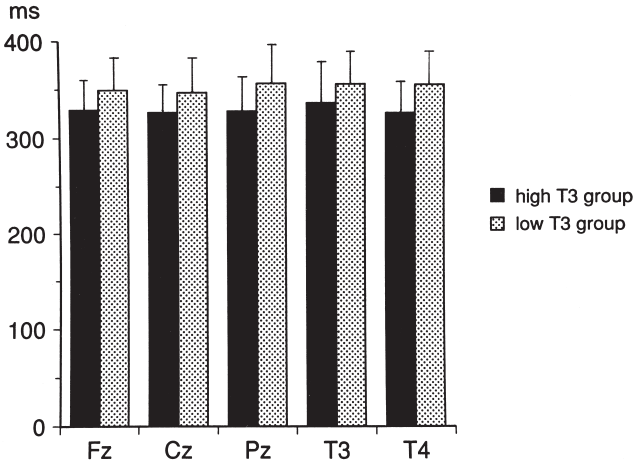

Fig. 3 Means and standard deviations of the P300 latency in the high and low T3 groups.

group effect ($F[1, 88]=2.998$, $p < 0.1$) and an electrode site effect ($F[2, 88]=21.435$, $p < 0.0001$), and in the lateral ANOVA there was a group effect ($F[1, 88]=4.993$, $p < 0.05$), and a trend for an electrode site effect ($F[1, 88]=2.936$, $p < 0.1$), and an interaction effect between the group and electrode site ($F[1,88]=73.742$, $p < 0.001$). For the P300 latency, there was a group effect in the overall ($F[1, 88]=10.425$, $p < 0.01$), and in the midline ($F[1, 88]=8.315$, $p < 0.01$), and in the lateral ANOVA ($F[1, 88]=7.183$, $p < 0.01$). These findings indicated that the patients in the low T3 group had relatively lower P300 amplitude and significantly delayed P300 latency, compared with those in the high T3 group.

Correlations between ERP components and clinical measures

Pearson product moment coefficiencies were calculated between the ERP variables and clinical measures (age, age at onset, duration of illness, daily dosage, and BPRS total score) in the patients. Although there were no other significant correlations between ERP variables and clinical measures, the P300 amplitude at T3 correlated significantly with age ($r=-.255$, $df=55$, $p < 0.05$) and BPRS total score ($r=-.270$, $df=55$, $p < 0.05$).

PCA

PCA for the waveforms of target stimuli were used to quantify the findings of the group differences in the P300 component. The database for the PCA consisted of 1440 waveforms (90 subjects x 16 electrode sites). First, 6 factors extracted by the PCA accounted for 86.4% of the variance. A Varimax rotation was performed on these 6 factors. The 6 factors obtained following the Varimax rotation are displayed in Fig. 4, in which the factor loadings are plotted against the time span of the analysis epoch. Factor 3, with a peak loading at a latency of 320 ms, is associated with the P300 component.

Repeated measures ANOVA was performed for the factor scores of Factor 3. In the overall ANOVA, there was a group effect ($F[1, 88]=15.426$, $p < 0.001$), an electrode site effect ($F[4, 88]=34.155$, $p < 0.0001$), and an interaction effect between the group and electrode site ($F[4,88]=4.883$, $p < 0.001$). In the midline ANOVA there was a group effect ($F[1, 88]=16.852$, $p < 0.0001$) and an electrode site effect ($F[2,88]=44.479$, $p < 0.0001$). In the lateral ANOVA, there was a group effect ($F[1, 88]=9.905$, $p < 0.01$) and a trend for an electrode site effect ($F[4, 88]=2.803$, $p < 0.1$). The findings of PCA did not indicate a topographical difference in P300 between patients and controls.

SCD mapping

SCD mappings for the P300 peak latency at Pz for schizophrenic patients and normal controls are shown in Fig. 5. These mappings suggest that the topographical patterns of the two groups cannot be clearly differentiated for P300.

Discussion

To examine the findings of P300 asymmetry over temporal regions in schizophrenic patients, we investigated the P300 of 57 patients and 33 controls. The P300 amplitude at T3 was not significantly smaller than that at T4 in schizophrenic patients, and in the ANOVA analysis of P300 peak amplitude and PCA factor scores, no significant lateral topographical difference in P300 was observed between patients and controls. However, in schiz-

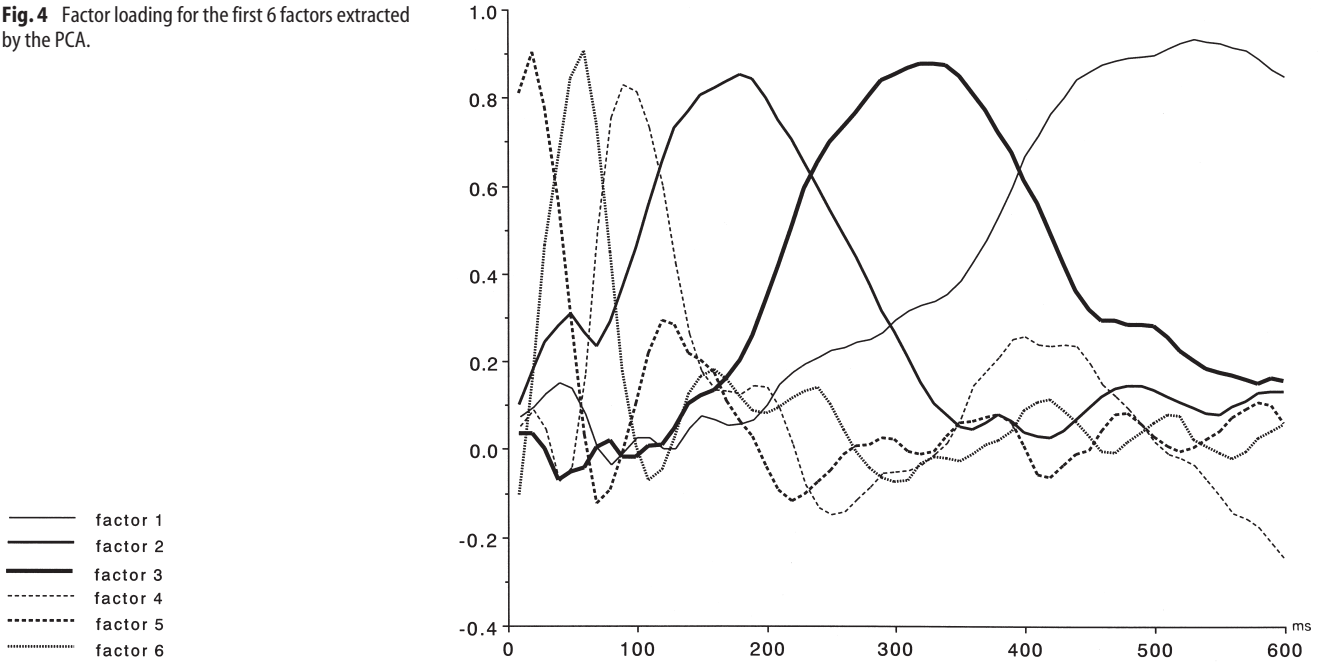

Fig. 4 Factor loading for the first 6 factors extracted by the PCA.

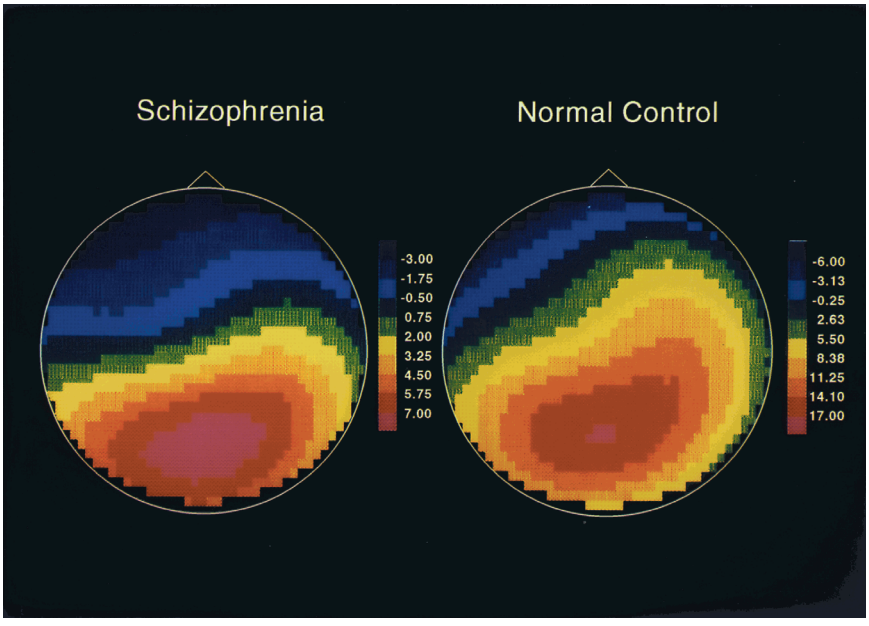

Fig. 5 SCD mapping ($\mu A/m^3$)for the P300 peak latency at Pz for schizophrenic patients (350 ms) and normal controls (317.5 ms).

ophrenic patients, those in the low T3 group were older and consuming higher doses of antipsychotic medicine than those in the high T3 group, and they had relatively lower P300 amplitudes and significantly delayed P300 latencies, compared with those in the high T3 group. Although the mean daily dosage for the low T3 group was significantly higher than that for the high T3 group, it was suggested that the effect of antipsychotic medication on the P300 indices might be minimal, since there was no significant correlation between the mean daily dosage and the P300 indices. Accordingly, the findings of the present study suggested that although the reduction in the left temporal P300 amplitude did not necessarily exist in schizophrenic patients, it may be associated with the severity of the disease process and/or impairment of cognitive function.

These results appear to be similar to those of Hill and Weibrod (1999). They recorded the P300 of 60 schizophrenic patients and 53 controls and noted that although a left hemispheric amplitude reduction was not a general feature of schizophrenics, low general P300 amplitudes were assigned to the left hemispheric amplitude reduction, and high amplitudes to the right hemispheric reduction. Moreover, Strik et al. (1994) reported that the left-right position of the P300 maximum was correlated with the P300 value at Pz. Accordingly, there

may be the possibility that the left P300 amplitude reduction is a biological marker of the severity and/or impairment of cognitive function of the disease.

The finding that the left temporal reduction of the P300 amplitude was not observed in schizophrenics is in contrast with some previous findings. McCarley and his colleagues have argued that left temporal reduction of the P300 amplitude was specific to schizophrenics. They reported that this finding was observed in schizophrenic patients but not in manic and first-episode depressive patients (Salisbury 1998, 1999). Moreover, they showed that gray matter volume reductions in the left superior temporal gyrus (STG) were associated with both P300 amplitude reduction and left < right topographic asymmetry (McCarley et al. 1993).

This inconsistency may result from the response mode. Many of the studies using silent counting reported P300 asymmetry but studies using a button press did not necessarily find it, as Salisbury noted (Salisbury 1998). Due to the use of button pressing, P300 asymmetry may not have been observed in the present study. Future experiments using plural response modes should be performed to clarify this point. Concerning the recording reference, although we used linked earlobes as the reference to compare the results of the present study with those of previous studies, this procedure might distort the measured electrical field. Further studies should be conducted without using linked recording references.

In a review of the significance of P300 in the pathophysiology of schizophrenia, Ford (1999) stated that P300 is both a state and a trait marker of the disease and may be sensitive to the progressive/degenerative course of the disease. With regard to the relationships between P300 and the clinical variables, the P300 amplitude reduction in schizophrenia has been reported to be associated with the severity of psychopathology, especially thought disorder (Iwanami et al. 2000), brain structure (Egan et al. 1994), neurodevelopmental disturbance (Hegerl et al. 1995), disability in daily life (Iwanami et al. 1999), and other clinical variables. However, these findings were not fully consistent between studies. In previous studies concerning the P300 in schizophrenics, the midline P300 was mainly examined. To use P300 as a diagnostic measure in clinical settings, it is necessary to examine the relationship between the left temporal P300 reduction and the longitudial clinical course and other psychophysiological and neuropsychological variables in schizophrenics in future studies. As Ford (1999) pointed out, it is obvious that instead of self-reported symptoms, to provide reliable biological markers for the diagnosis of schizophrenia may lead to better treatment of the disease.

In conclusion, from the results of the present study it is suggested that the left temporal P300 reduction is not a general feature of schizophrenia, but it might reflect the severity and/or cognitive impairment of the disease. Pfefferbaum et al. (1991) suggested that the inconsistency concerning the P300 asymmetry may be associated with differences in the patient populations. To further clarify the cause of the inconsistency of previous studies, investigations using patients with a variety of severity should be preformed.

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