[原著] Abnormal Fronto-Temporal Network in First-Episode Schizophrenia Revealed by Low-Resolution Electromagnetic Tomography (LORETA) of P300 Auditory Event-Related Potentials

Abnormal Fronto-Temporal Network in First-Episode Schizophrenia Revealed by Low-Resolution Electromagnetic Tomography (LORETA) of P300 Auditory Event-Related Potentials

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ABSTRACT

The P300 component of auditory event-related potentials (ERPs) is an electrophysiological marker of cognitive operation. Previous studies had found dysfunction of the fronto-temporal network in schizophrenia using P300 current density analysis. However, whether this abnormality is a primary effect of schizophrenia remains unclear, because chronic patients had been included in previous studies. In this study, P300 current density analysis was performed in 30 first-episode and drug-free schizophrenic patients and 30 normal controls. P300 was elicited using an auditory oddball paradigm. ERPs were recorded from 16 scalp electrodes. A new method of low-resolution electromagnetic tomography (LORETA) was applied to perform P300 current density analysis in this study. The cortical P300 sources were computed from grand average waveforms. A significant probability map of P300 cortical current density differences between two groups was constructed, based on the point-by-point t-test. The 3-D cortical current density map demonstrated activation of the bilateral fronto-temporal network as the major neural generator of the scalp-recorded P300 in control subjects. However, in schizophrenics, this activation was decreased as compared with control subjects. Furthermore, inter-group differences in P300 current density were more prominent over the left versus the right hemisphere. It is suggested that the dysfunction of the fronto-temporal network, especially over the left hemisphere, might be a primary effect of schizophrenia, possibly being involved in the mechanism of schizophrenia. *Ryukyu Med. J., 21(3,4) 143～150, 2002*

Key words: schizophrenia, LORETA, P300, ERPs, cortical current density

INTRODUCTION

The P300 component of the event-related potentials (ERPs) emerges at around 300 msec after presentation of an auditory stimulus and is considered to be an electrophysiological marker of cognitive operation[1, 2]. It has been widely applied in investigation of the cognitive deficits in schizophrenia. In clinical studies, the P300 has often been obtained using an auditory paradigm. A reduction of auditory P300 amplitude in schizophrenic patients has been reported by many investigators and is a consistent finding[3-5]. This abnormality is regarded as one of the most robust biological findings in schizophrenia. However, the abnormality is non-specific to schizophrenia, as it has also been found in other psychiatric populations, such as in subjects with schizotypal personality disorder, depression and alcoholism[6-9].

Efforts to better understand the P300 abnormality in schizophrenia have led to investigating the neural substrates among these patients. Studies of surface potential topography have found that the P300 amplitude reduction in schizophrenia is not uniformly distributed across the scalp. Left temporal scalp area reduction of P300 is more prominent than right in schizophrenic patients and this asymmetry is associated with a reduction in volume of the left superior temporal gyrus gray matter[10, 11]. However, the P300 scalp topography is not an exact

image of the neural activity during the task due to volume conduction effect.

Methodological improvements have been made to further clarify the neural substrates of P300 ab normality in schizophrenia. Recently, low-resolution electromagnetic tomography (LORETA) has been used to estimate the electric sources contributing to the scalp-recorded P300[12]. LORETA assumes that neighboring neurons are simultaneously and synchronously activated. Furthermore, LORETA computes the smoothest of all possible source configurations throughout the brain volume by minimizing the total squared Laplacian of source strengths, and estimates the electrical sources in the brain[13]. Through the use of LORETA, P300 sources were estimated to be over bilateral prefrontal cortex, the temporal lobe, the cingulum, the parieto-occipital junction, the inferior parietal cortex and the superior parietal cortex[12, 14]. These results are basically consistent with findings from intracranial recordings. LORETA analysis of P300 had also been per formed among schizophrenic patients by Winterer *et al.,* revealing that between 240-420 msec poststimulus, schizophrenic patients showed a less activated cortex mainly over the left hemisphere including the prefrontal cortex, posterior cingulum and the temporal lobe, as compared to the control subjects.

However, P300 in the LORETA study by Winterer *et al.* was elicited during an auditory choice reaction paradigm, in which the subjects were instructed to respond to two targets with the same probability. This paradigm is seldom applied in clinical studies, and is quite different from the extensively applied oddball paradigm, in which the subjects are instructed to count the infrequent targets embedded in a sequence of frequent non-targets. Since ERP components are sensitive to probability, the P300 component obtained from an oddball paradigm may reflect cognitive operation more clearly than that from an auditory choice reaction paradigm[15]. More importantly, although the patients in the study by Winterer et al. were drug-free, they were not all first-episode patients. The mean age of the patients in the study was 36.3 years and all were inpatients. Thus, the effect of illness chronicity and comorbidity on P300 abnormality had not been excluded[16].

The aim of this study was to investigate the neural basis of P300 abnormalities in schizophrenic patients using LORETA analysis. Previous P300 current density analysis of LORETA have been performed using a simplified spheric head and 3-D Talairach space[12-14], but the 3-D cortical images of P300 generators have not been well demonstrated. In this study, the current density results were mapped on the cortical surface of a general head model to construct the cortical 3-D maps of P300 current density.

MATERIALS AND METHODS

(1) Subjects

All subjects were right-handed, as determined by the handedness questionnaire of Raczkowski *et al.*[17] Thirty schizophrenic patients (20 men and 10 women) were recruited from the University of the Ryukyus Hospital and its affiliated hospitals. Mean age and SD were 25.8 ± 8.2.

All the patients met the DSM-IV criteria for schizophrenia, as diagnosed by staff psychiatrists. The diagnosis was confirmed at a case conference. All of them were first-episode schizophrenia. Seventeen of the patients had never received neuroleptic treatment, while 13 had been treated with antipsychotic medication, but had not received neuroleptic medication for a minimum of 4 weeks prior to the study. A normal control group consisting of 30 individuals (15 men and 15 women) was recruited from the community and hospital staff. Mean age and SD were 25.3 ± 7.9. None of the control subjects had psychiatric histories. All subjects, including schizophrenic patients, were free of neurological diseases, mental retardation and physical illness that might affect cognitive function or produce hearing loss. All of the subjects gave informed consent before the experiment.

(2) ERP Recordings

Auditory ERPs were recorded using an 'oddb all' task. Stimuli consisted of a 1 kHz tone burst (frequent non-target stimulus) and a 2 kHz tone burst (rare target stimulus). The respective probabilities of the rare and frequent stimuli were 0.2 and 0.8. Stimuli were presented in random order, the duration of each being 90 msec, with rise and fall times of 10 msec. Stimuli were presented in random order at a speaker sound level of 75 dB. The interstimulus interval was 1.7 ± 0.1 sec. Forty artifact-free repetitions were averaged. Participants were instructed to count silently the number of rare

tones and to report their count after each run. Scalp EEGs were recorded from 16 Ag-AgCl disk electrodes (Fp1, Fp2, F7, F3, Fz, F4, F8, C3, C4, T5, T6, P3, Pz, P4, O1 and O2) according to the International 10-20 system with a linked earlobe reference. Electrode impedance was maintained at less than 5 kΩ. The electrooculograms (EOGs) were obtained from electrodes placed above and below the right eye. Amplifiers required a bandpass of 0.16 (time constant = 1.0 sec) to 30 Hz. The EEGs and EOGs were sampled at a rate of 1 msec per point using a laboratory computer (NEC-SANEI, Japan, DP-1200). A/D conversion was done from 200 msec before to 800 msec after stimulus onset with a sampling time of 1 msec per point. ERPs were averaged separately for the rare and frequent stimuli. Trials were automatically omitted from the averaging if the voltage exceeded ± 100 μV in the EOG lead. The averages of the potentials were set to a baseline mean potential of the 200 msec period preceding stimulus onset.

(3) Data Analysis

The ERP data were exported as ASCII data, and the ERP voltages were transformed into reference-independent values by recomputation of the voltage value's averaged reference[12]. The global field power (GFP) was calculated for individual target ERPs using the following formula[18]: GFP = root mean square (RMS) = $[\Sigma(\text{voltage of 16 electrodes})^2/16]^{1/2}$. According to the GFP curves, P300 latency was defined as the maximal GFP peak within 250-450 msec.

Cortical current density of P300 was analyzed by LORETA at the point of P300 latency defined by the maximal GFP of the P300 component. LORETA data was processed and analyzed using Curry 4.01 software (Neuroscan Labs., Neurosoft Inc.). The head model was a realistic volume conductor model (skin: 12 mm, skull: 10 mm, liquor: 8 mm) made by a boundary element method. The location of each electrode on the scalp was set in 3-D coordinates corresponding to the International 10-20 system. The spatiotemporal data of scalp potentials were then converted to current density using Laplacian second derivatives. The distance between the three-dimensional grid points in the brain model was 13 mm. Current densities were distributed smoothly as 6222 points on the cortex model. Smoothed current densities were then overlapped on the cortical model utilized for the template in this software as a standard model consisting of 39222 voxels.

In addition to determining the current densities among individuals, we also analyzed the grand average ERP waveforms of both groups by using LORETA. These grand average waveforms were synchronized to the moment of maximal GFP of the P300 components in the target waveform.

Statistical group comparisons of the P300 latency and the maximal GFP of P300 were performed by t-test. The LORETA current densities on 6222 points among all participants were tested by point-by-point t-test between the control and schizophrenic patient groups.

RESULTS

(1) ERP waveforms and GFP

The grand average ERP waveforms by rare stimuli at Fz and Pz for 30 controls and 30 schizophrenic patients are shown in Figure 1. After stimulus onset, the first negative-going peak at about 100 msec is N100. It is followed by another large positive peak at about 300 msec, the P300 component. Visual inspection showed a reduction of P300 amplitude and a prolongation of P300 latency in schizophrenic patients as compared to controls.

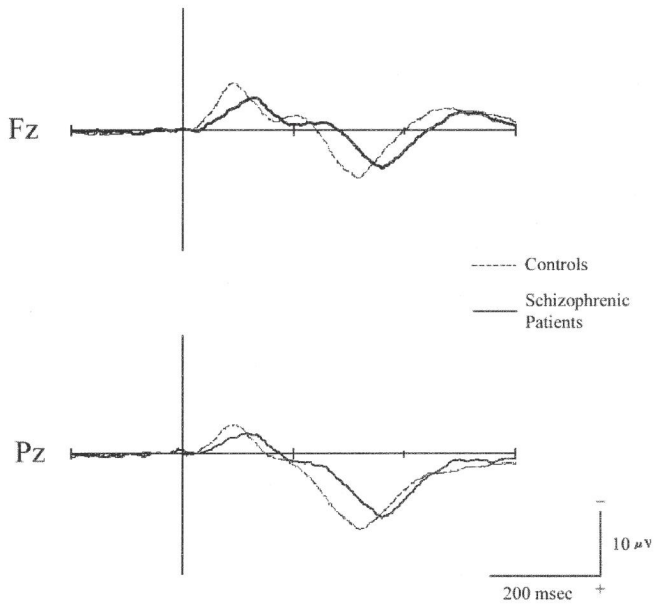

Fig. 1 The grand average waveforms of ERPs at Fz (top) and Pz (botttom) for the 30 controls and 30 schizophrenic subjects by the rare stimuli. Dotted lines show ERPs from controls and solid lines from schizophrenic patients.

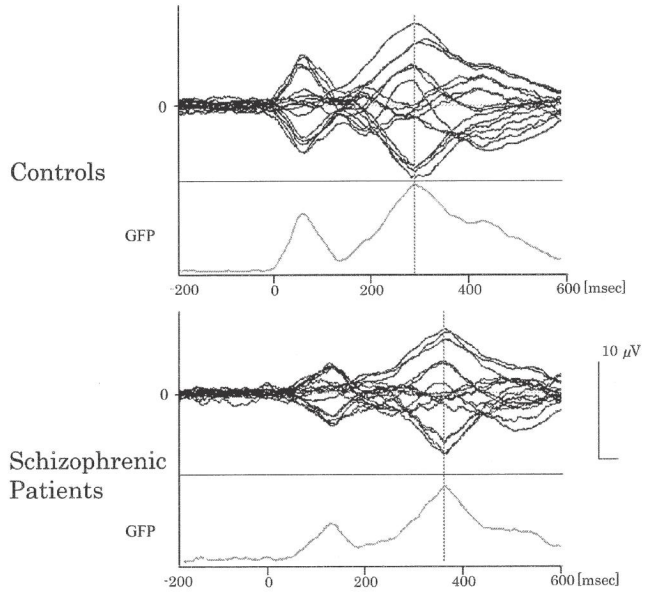

Fig. 2 Grand mean ERP waveforms with regard to average reference at 16 electrodes and GFP curves in controls and schizophrenic patients. These ERP waveforms of both groups were synchronized to the moment of maximal GFP of the P300 components in the target waveform. These broken lines indicate each point of the maximal GFP peak within 250 - 450 msec post-stimulus (controls: 310.8 msec, schizophrenic patients: 355.9 msec).

Figure 2 shows grand mean target ERP waveforms with regard to average reference at 16 electrodes and the corresponding GFP curve in controls and schizophrenic patients. There was a large peak corresponding to P300 between 250 and 450 msec in each GFP curve. From this peak, the maximal GFP (RMS) value and the latency of maximal GFP of the P300 component were calculated. The maximal P300 GFP value was lower in patients than in controls (patient group: 7.28 ± 3.1 μ V; control group: 9.36 ±3.2 μ V; F = 6.4, p = 0.014). The mean latency of maximal GFP of the P300 component was longer in patients than in controls (patient group: 355.9 ± 35.9msec; control group: 310.8 ± 26.4msec; F = 30.7, p<0.001).

(2) Cortical maps of P300 current density

The cortical maps of P300 current density were computed using the grand average waveforms for each group, and are shown in Figure 3. During the oddball paradigm, the neural activity was activated mainly over bilateral frontal and temporal areas in the control group, demonstrating that the fronto-temporal network was activated bilaterally in this group. In the patient group, the activation of the bilateral front-temporal regions was detectable, but the activated areas were visually smaller and weaker than in the control group.

(3) Significant probability map of P300 cortical current density

The inter-group difference of P300 current density was assessed point-by-point using the t-test. Based on these results, the significant probability

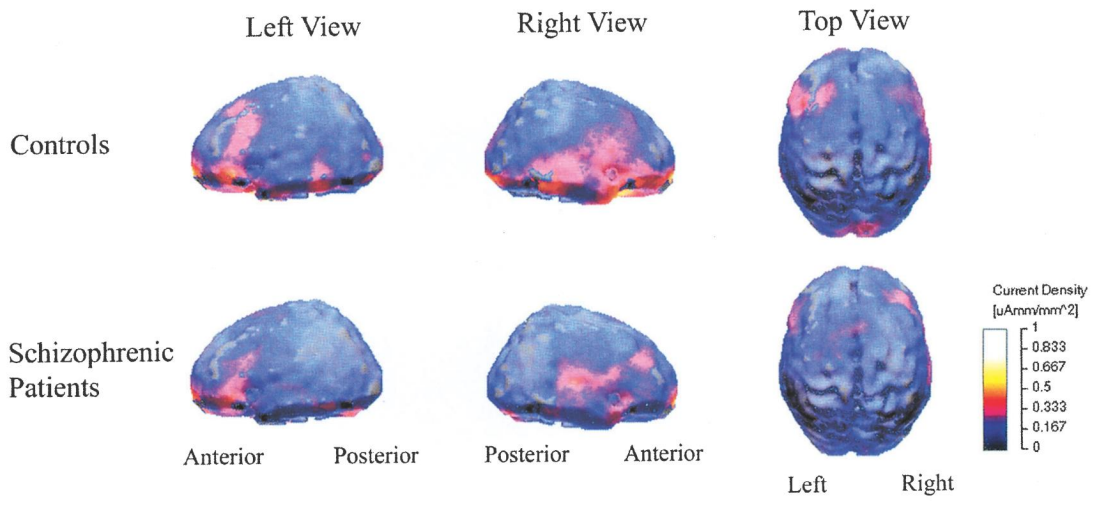

Fig. 3 Cortical current density map of P300 generated by LORETA in controls and schizophrenic patients. LORETA analysis was applied to the grand average ERP waveforms of both groups. The portion shown by warm color indicates greater activity.

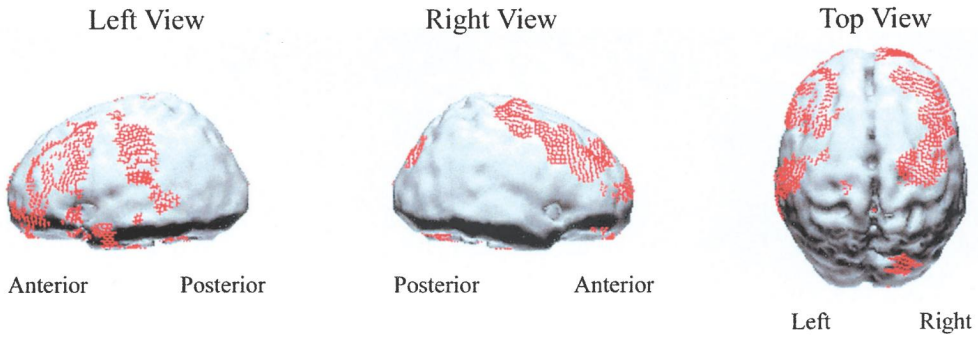

Fig. 4 Significant probability map of P300 cortical current density differences between controls and schizophrenic patients. Results of point-by-point t-test were reconstructed on a 3-D cortical surface map. P-values of less than 0.05 are indicated in red.

maps of P300 cortical current density difference between the two subject groups were constructed, and are shown in Figure 4. All points at which the inter-group difference was significant ($P<0.05$) have been marked. It is very clear that the inter-group difference of P300 current density is concentrated over the fronto-temporal cortex. While the difference of P300 current density was bilaterally distributed over the frontal cortex, it was limited to the left hemisphere versus the right hemisphere over the temporal cortex.

DISCUSSION

P300 cortical current density, as determined by LORETA in the present study, indicated P300 related cortical activation over the frontal and temporal regions in controls, demonstrating the activation of a bilateral fronto-temporal network during the oddball paradigm. Compared with the control subjects, schizophrenic patients showed a less activated bilateral fronto-temporal network during the P300 task, and showed this abnormality more prominently over the left than over the right hemisphere. Results from this study are basically consistent with previous LORETA studies performed in schizophrenic patients as well as in controls[12-14]. In this study, the cortical activation of bilateral parieto-occipital areas was not as remarkable as in those previous studies, possibly due to the 3D-cortical maps of P300 current density having been constructed using grand average waveforms. However, because all individual ERP waveforms had been synchronized to the moment of maximal GFP of the P300 components in the target grand average waveform, the authors argued that the bilateral parieto-occipital cortex might be a minor P300 neural generator. Whereas Winterer et al. reported in their study more cortical areas as the scalp P300 generators, their use of a time range of 240-420 msec poststimulus to perform LORETA analysis, the group difference of P300 current density between schizophrenic patients and controls was relatively limited to the prefrontal cortex, posterior cingulum and the temporal lobe. Except for the posterior cingulum, both the dysfunctional fronto-temporal cortex and the left-right asymmetry of this abnormality were confirmed in the present study; however the posterior cingulum could not be detected in the head model used in the present study so confirmation was impossible at the time of analysis.

In the study by Winterer et al., patients were selected with an emphasis on their drug-treatment history[14]. Although the illness duration of their patients was not stated, it is very likely that some chronic patients were included. The mean age of their patients was 36 ± 11 years, far older than that of the present study (26 ± 8 years). In chronic patients, factors undermining the significance of neurobiological findings are very complicated. Long illness duration has been correlated with more severe P300 abnormality in chronic schizophrenic patients[19-21]. While the effect of some comorbidity (for instance, tardive dyskinesia) on the P300 component has been reported[22], the effect of some other comorbidities (i.e., high nicotine dependence) on P300 has not yet been studied. In addition, 2 patients being kept drug-free for 3 days were also included in Winterer's study. A period of 3 days is too short to exclude the neuroleptic effect.

This is the first study, in which the LORETA analysis of the P300 component was performed

among first-episode schizophrenic patients. Schizophrenia is a lifetime neuropsychiatric disorder. The early course of schizophrenia is the most important period in the development of chronicity. It has been suggested that the primary neurobiological deficit processes of the disorder may exist in the first-episode patients[23].

In ERPs study, the present study extended the investigation of the P300 related dysfunctional fronto-temporal network and the asymmetry of this abnormality, previously reported in chronic and/or medicated schizophrenia patients[24], to first-episode patients who were at the early stage of the illness. The authors suggest that these neurobiological abnormalities are possibly primary effects of schizophrenia rather than effects secondary to illness duration or neuroleptic treatment, and are therefore involved in the mechanism of schizophrenia. Our study is in line with two other ERPs studies performed among first-episode patients. Salisbury et al. replicated the left-to- right asymmetry of temporal P300 reduction in their medicated first-episode patients[25]. Demiralp et al. reported that, in contrast to a widespread decrease in chronic patients, P300 amplitude reduction occurred most prominently over the frontal areas in first-episode patients[26]. Recent MRI volumetric studies suggested that anatomical abnormalities are present during the early stage of illness in patients with first-episode schizophrenia. The affected brain structures include the frontal lobe, temporal lobe and hippocampus, which are also involved in the generation of P300[27, 28].

The limitation of LORETA analysis constituted the limitation of this study. Just as its name implies, LORETA can not make high-resolution solutions, and sometimes makes a localization error of two or three voxels. However, to our knowledge, there is no better way than LORETA to infer the neural substrates from the scalp-recorded ERP data [29]. LORETA can be used as a valuable means to indicate the generator locations, especially when prior knowledge of neural mechanisms is not available. In future studies, the "low resolution" problem could be resolved by collecting ERP data using a high density recording; restricting the solution space to individual MRI volume image, etc.

In summary, P300 cortical current density of first-episode schizophrenia was decreased over the fronto-temporal area with a bias toward the left versus the right hemisphere. It is suggested that the P300 related dysfunction of the fronto-temporal network, especially over the left hemisphere, might be a primary effect in schizophrenia, possibly being involved in the mechanism of schizophrenia.

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REFERENCES

1) Donchin E.: Presidential address, 1980. Surprise!...Surprise? Psychophysiology. 18: 493-513, 1981.
2) Hillyard S.A., Hink R.F., Schwent V.L. and Picton T.W.: Electrical signs of selective attention in the human brain. Science. 182: 177-80, 1973.
3) Pritchard W.S.: Cognitive event-related potential correlates of schizophrenia. Psychol. Bull. 100: 43-66, 1986.
4) Ogura C., Nageishi Y., Matsubayashi M., Omura F., Kishimoto A. and Shimokochi M.: Abnormalities in event-related potentials, N100, P200, P300 and slow wave in schizophrenia. Jpn. J. Psychiatry Neurol. 45: 57-65, 1991.
5) Hirayasu Y., Asato N., Ohta H., Hokama H., Arakaki H. and Ogura C.: Abnormalities of auditory event-related potentials in schizophrenia prior to treatment. Biol. Psychiatry. 43: 244-53, 1998.
6) Mannan R., Hiramatsu K., Hokama H. and Ohta H.: Abnormalities of auditory event-related potentials in students with schizotypal personality disorder. Psychiatry Clin. Neurosci. 55: 451-7, 2001.
7) Blackwood D.H.R., Whalley L.Y., Christie J.E., Blackburn J.M., St-Clair D.M. and Mcinnes A.: Changes in auditory P3 event-related potential in schizophrenia and depression. Br. J. Psychiatry. 150: 154-60, 1987.
8) Pfefferbaum A., Enegrat B., Ford J.M., Roth W.T. and Kopell B.S.: Clinical application of event-related potentials. Ⅱ. Dementia, depression and schizophrenia. Electroenceph. Clin. Neurophysiol. 59: 104-24, 1984.
9) Pfefferbaum A., Ford J.M., White P.M. and

Mathalon D.H.: Event-related potentials in alcoholic men: P3 amplitude reflects family history but not alcohol consumption. Alcohol Clin. Exp. Res. 15: 839-50, 1991.
10) McCarley R.W., Shenton M.E., O'Donnell B.F., Faux S.F., Kikinis R., Nestor P.G. and Jolesz F.A.: Auditory P300 abnormalities and left posterior superior temporal gyrus volume reduction in schizophrenia. Arch. Gen. Psychiatry. 50: 190-7, 1993.
11) Salisbury D.F., Shenton M.E. and McCarley R.W.: P300 topography differs in schizophrenia and manic psychosis. Biol. Psychiatry. 45: 98-106, 1999.
12) Anderer P., Pascual Marqui R.D., Semlitsch H.V and Saletu B.: Electrical sources of P300 event-related brain potentials revealed by low resolution electromagnetic tomography. 1. Effects of normal aging. Neuropsychobiology. 37: 20-7, 1998.
13) Pascual Marqui R.D., Michel C.M. and Lehmann D.: Low resolution electromagnetic tomography: a new method for localizing electrical activity in the brain. Int. J. Psychophysiol. 18: 49-65, 1994.
14) Winterer G., Mulert C., Mientus S., Gallinat J., Schlattmann P., Dorn H. and Herrmann W.M.: P300 AND LORETA: comparison of normal subjects and schizophrenic patients. Brain Topogr. 13: 299-313, 2001.
15) Picton T. W. and Stuss T.D.: The component structure of the human event-related potentials. Prog. Brain Res. 54: 17-48, 1980.
16) Manthalon D.H., Ford J.M. and Pfefferbaum A.: Trait and state aspects of P300 amplitude reduction in schizophrenia: a retrospective longitudinal study. Biol. Psychiatry. 47: 434-49, 2000.
17) Raczkowski D., Kalat J.W. and Nebes R.: Reliability and validity of some handedness questionnaire items. Neuropsychologia. 12: 43-7, 1974.
18) Lehmann D. and Skrandies W.: Reference-free identification of components of checkerboard-evoked multichannel potential fields. Electroencephalogr. Clin. Neurophysiol. 48: 609-21, 1980.
19) O'Donnell B.F., Faux S.F., McCarley R.W., Kimble M.O., Salisbury D.F., Nestor P.G., Kikinis R., Jolesz F.A. and Shenton M.E.: Increased rate of P300 latency prolongation with age in schizophrenia. Electrophysiological evidence for a neurodegenerative process. Arch. Gen. Psychiatry. 52: 544-9, 1995.
20) Olichney J.M., Iragui V.J., Kutas M., Nowacki R., Morris S. and Jeste D.V.: Relationship between auditory P300 amplitude and age of onset of schizophrenia in older patients. Psychiatry Res. 79: 241-54, 1998.
21) Mathalon D.H., Judith M., Rosenbloom M. and Pfefferbaum A.: P300 reduction and prolongation with illness duration in schizophrenia. Biol. Psychiatry. 47: 413-27, 2000.
22) Hegerl U., Juckel G., Muller-Schubert A., Pietzcker A. and Gaebel W.: Schizophrenics with small P300: a subgroup with a neurodevelopmental disturbance and a high risk for tardive dyskinesia? Acta Psychiatr. Scand. 9: 120-5, 1995.
23) McGlashan T.H.: Duration of untreated psychosis in first-episode schizophrenia: marker or determinant of course? Biol. Psychiatry. 46: 899-907, 1999.
24) Turetsky B.I., Colbath E.A. and Gur R.E.: P300 subcomponent abnormalities in schizophrenia: I. Physiological evidence for gender and subtype specific differences in regional pathology. Biol. Psychiatry. 43: 84-96, 1998.
25) Salisbury D.F., Shenton M.E., Sherwood A.R., Fischer I.A., Yurglun-Told D.A. and Tohen M.: First-episode schizophrenic psychosis differs from first affective psychosis and controls in P300 amplitude over left temporal lobe. Arch. Gen. Psychiatry. 55: 173-80, 1998.
26) Demiralp T., Ucok A., Devrim M., Isoglu-Alkac U., Tecer A. and Polich J.: N2 and P3 components of event-related potential in first-episode schizophrenic patients: scalp topography, medication, and latency effects. Psychiatry Res. 111: 167-79, 2002.
27) Hirayasu Y., Shenton M.E., Salisbury D.F., Dickey C.C., Fischer I.A., Mazzoni P., Kisler T., Arakaki H., Kwon J.S., Anderson J.E., Yurgelun-Todd D., Tohen M. and McCarley R.W.: Lower left temporal lobe MRI volumes in patients with first-episode schizophrenia compared with psychotic patients with first-episode affective disorder and normal subjects. Am. J. Psychiatry. 155: 1384-91, 1998.
28) Hirayasu Y., Tanaka S., Shenton M.E., Salisbury D.F., DeSantis M.A., Levitt J.J., Wible C., Yurgelun-Todd D., Kikinis R., Jolesz F.A. and McCarley R.W.: Prefrontal gray matter volume

reduction in first episode schizophrenia. Cereb. Cortex. 11: 374-81, 2001.
29) Pascual-Marqui R.D., Esslen M., Kochi K. and Lehmann D.: Functional imaging with low resolution brain electromagnetic tomography (LORETA): review, new comparisons, and new validation. Jpn. J. Clin. Neurophysiol. 30: 81-94, 2002.