International Journal of Psychophysiology 75 (2010) 249–257

Contents lists available at ScienceDirect

International Journal of Psychophysiology

journal homepage: www.elsevier.com/locate/ijpsycho

Decreased P300 current source density in drug-naive first episode schizophrenics revealed by high density recording

Jijun Wang [a], Yunxiang Tang [b,*], Chunbo Li [a,*], Axel Mecklinger [c], Zeping Xiao [a], Mingdao Zhang [a], Yoshio Hirayasu [d], Hiroto Hokama [e], Hui Li [a]

[a] Shanghai Mental Health Center, Shanghai Jiaotong University School of Medicine, Shanghai 200030, China
[b] Department of Psychology, Faculty of Health Service, Second Military Medical University, Shanghai 200433, China
[c] Experimental Neuropsychology Unit Postfach 151150, D-66041 Saarbrücken, Germany
[d] Department of Psychiatry, Yokohama City University School of Medicine, Yokohama, Japan
[e] Department of Psychiatry, the University of Ryukyus, Okinawa, Japan

ARTICLE INFO

Article history:
Received 16 May 2009
Received in revised form 25 November 2009
Accepted 3 December 2009
Available online 24 December 2009

Keywords:
First episode schizophrenia
P300
Low resolution of electromagnetic tomography (LORETA)

ABSTRACT

Decreased P300 amplitude has been reported in schizophrenics during their first episode. The brain sources that contribute to this abnormality have not yet been well documented, and were investigated in the present study using high density EEG recordings. Nineteen drug-naive first episode schizophrenics were compared to 25 normal controls. Auditory P300 was elicited using an oddball paradigm. The brain sources of P300 ERP were reconstructed by performing low resolution of electromagnetic tomography (LORETA) analysis. No group difference in P300 latency was found. P300 amplitude was smaller for schizophrenics than for controls. Topographical analysis revealed that P300 amplitude reduction in schizophrenics was significant over left and medial regions of interest (ROIs). LORETA analysis of the P300 peak revealed that, the brain sources of P300 were symmetrically distributed over left and right hemispheres among the normal controls, but were asymmetrically distributed among the patients, with a reduction predominantly over the left temporal area. Statistical non-Parametric Mapping analysis identified 29 voxels of a significant group difference, which focused on left insula, left superior temporal gyrus (STG) and left postcentral gyrus (PCG). In addition, the mean P300 current source density over left insula, left STG and left PCG correlated inversely with the patients' Positive and Negative Syndrome Scale scores. The neural substrates that contributed to the decreased P300 amplitude in drug-naive first episode schizophrenia relatively focused on left STG and its nearby areas. These areas are probably involved in the pathogenesis of schizophrenia, and possible mechanisms for pathology need to be further clarified.

1. Introduction

Schizophrenia is a complex disorder, and its pathophysiology is best understood through the findings from first episode schizophrenia patients, mainly because confounding factors such as chronic morbidity, neuroleptic medication and/or hospitalization among chronic patients, and are difficult to disentangle from the disease process.

Cognitive deficits are one of the core features of schizophrenia and have been investigated using P300 of auditory event-related potentials (ERPs) for several decades. However, the history of P300 study of first episode schizophrenia is only about 10 years old. The characteristics of P300 abnormalities in first episode schizophrenia are similar to, but not identical to, those previously reported among patients with a more chronic course. Almost all studies have found P300 amplitude reduction among first episode schizophrenia patients (Hirayasu et al., 1998; Salisbury et al., 1998; McCarley et al., 2002; Brown et al., 2002; Demiralp et al., 2002; Wang et al., 2003b, 2005; van der Stelt et al., 2005; Renoult et al., 2007; Ozgürdal et al., 2008). Decreased P300 amplitude was also found among individuals clinically at risk for psychosis (Frommann et al., 2008; Ozgürdal et al., 2008). Regarding P300 latency, while Demiralp et al. (2002) reported P300 latency prolongation in first episode patients, Wang et al. (2003b) found an increased rate of P300 latency prolongation with age in drug-naive first episode schizophrenia. These results support the idea that auditory P300 abnormalities in schizophrenia might reflect a primary pathophysiological feature of the illness.

In first episode schizophrenia patients, smaller P300 amplitude over the left temporal area has been associated with smaller left superior

* Corresponding authors. Tang is to be contacted at Department of Psychology, Faculty of Health Service, Second Military Medical University, Shanghai 200433, China. Li, Department of Biological Psychiatry, Shanghai Mental Health Center, Shanghai Jiaotong University School of Medicine, Shanghai 200030, China. Tel.: +86 21 6438 7250 3065; fax: +86 21 6438 7986.
E-mail addresses: oukeigun@yahoo.com.cn, tangyunxiang1973@tom.com (Y. Tang), chunbo_li@163.com (C. Li).

0167-8760/$ – see front matter. Crown Copyright © 2009 Published by Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpsycho.2009.12.005

temporal gyrus (STG) gray matter volume on magnetic resonance imaging (MRI) (McCarley et al., 2002). To better understand the P300 abnormalities in first episode schizophrenia it is important to investigate its neural substrates.

Topographical studies have revealed two components of P300, P3a and P3b (Soltani and Knight, 2000). The P3b, elicited by target stimuli and recorded in most clinical settings, often shows its topographical distribution with a maximum over the parietal regions (Katayama and Polich, 1998). It reflects the match between the incoming stimulus and the voluntarily maintained attentional trace of the task relevant stimulus. The P3a, elicited by rare non-target stimuli, demonstrates its topographical distribution with a more anterior distribution than the P3b. The P3a is thought to represent the automatic attentional switch to deviant stimuli or distractors with respect to the ongoing task (Goldstein et al., 2002). Intracranial investigations have shown that the P3a generators are located in the anterior cingulate and fronto-parietal cortex and the P3b generators in superior temporal, posterior parietal, hippocampal, cingulate and frontal structures (Halgren et al., 1995a,b, 1998). However, the intracranial recordings are not suitable for investigations involving healthy volunteers or psychiatric patients. Recently, the neural basis of P300 has been investigated using non-invasive functional magnetic resonance imaging (fMRI) by several studies, which confirmed the involvement of the frontal, parietal, temporal and cingulate areas in the genesis of P300 ERP (Mulert et al., 2004; Stevens et al., 2006). One limitation of fMRI technique in the identification of brain generators of P300 is its relatively poor temporal resolution.

Electrophysiological techniques have a far better temporal resolution, and a new method of low resolution brain electromagnetic tomography (LORETA) has been developed for reconstructing the current source for a given scalp electrical distribution in recent years (Pascual-Marqui et al., 1994). LORETA does not require the assumption of a specific number of sources, and only assumes that neighboring neurons are simultaneously and synchronously activated and approximates the current density distribution throughout the brain (Pascual-Marqui et al., 1994). Validation of LORETA has been made by comparing its findings with those by intracranial recordings (Lantz et al., 1997). Consistency between LORETA and neuroimaging studies has been reported. Strik et al. (1998) used LORETA to identify frontal activation as the electrical generators of the P300 produced during a cued continuous performance test, which is consistent with the findings by previous positron emission tomography studies. The electrical sources of ictal EEG discharges revealed by LORETA were consistent with the results from well-defined symptomatic MRI lesions (Worrell et al., 2000). The time-course of activations corresponding to P300 ERP has been investigated using both LORETA and fMRI (Mulert et al., 2004), and the LORETA findings were well consistent with those provided by fMRI. Through use of LORETA, P300 sources were estimated to occur over bilateral prefrontal cortex, the temporal lobe, the cingulum, the parieto-occipital junction, the inferior parietal cortex and the superior parietal cortex (Anderer et al., 1998; Winterer et al., 2001; Wang et al., 2003a; Volpe et al., 2007). It is suggested that the main regions consistently attributed to generating P300 related brain activation include the temporal–parietal junction, medial–temporal complex, and the lateral prefrontal cortex (Soltani and Knight, 2000; Volpe et al., 2007).

Several studies had performed LORETA analysis to estimate the P300 neural sources among schizophrenia patients (Winterer et al., 2001; Wang et al., 2003a; Pae et al., 2003; Sumiyoshi et al., 2006; Kawasaki et al., 2007; Higuchi et al., 2008). Most of these studies consistently demonstrated that the affected P300 neural sources were mainly over the left hemisphere. The P300 current source density (CSD) over the left superior temporal gyrus (STG) had been correlated with the Positive subscale score of the brief psychiatric rating scale (BPRS) (including item hallucinatory behavior, hostility, unusual thought content) and with the Negative subscale score of BPRS (including item blunted affect, emotional withdrawal, motor retardation) by Kawasaki et al. (2007). Higuchi et al. (2008) also found that a six-month treatment with olanzapine significantly increased P300 source density in the left STG, which correlated with improvements of negative symptoms and verbal learning memory. However, none of these studies used the first episode patients, with the exception of the study by Kleinlogel et al. (2007), in which the NoGo-P300 to the NoGo-stimuli during a visual Continuous Performance Test (CPT) was the main focus. Therefore, the neural sources of auditory P300 have not yet been investigated among first episode schizophrenia patients using LORETA.

The main purpose of the present study was to investigate auditory P300 neural sources among first episode schizophrenia patients. Because a short history of antipsychotic medication possibly influences the P300 ERP, only drug-naive patients were recruited. In addition, because both simulation and experimental studies clearly indicate that at least 60 equally distributed electrodes are needed to correctly sample the scalp electric field that is submitted to the source localization procedure (Michel et al., 2004), a high density recording of 60 channels was applied to record auditory P300 in the present study.

2. Methods

2.1. Subjects

All subjects participating in the study signed an informed consent for a protocol approved by the Institutional Review Board (IRB) of Shanghai Mental Health Center, Shanghai Jiaotong University. The patients were recruited from among those who first came to Shanghai Mental Health Center, Shanghai Jiaotong University, who met ICD-10 diagnostic criteria for schizophrenia (F20), and who had no history of antipsychotic medication use. Diagnosis verification was made by a senior psychiatrist at the rank of associate professor within two weeks. Nineteen drug-naive first episode schizophrenia patients were included in the present study. Clinical symptoms were evaluated using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). The control subjects were 25 healthy subjects, none of whom had a history of psychiatric illnesses. All the subjects, both the patients and healthy controls, were free of neurological disease, mental retardation, alcohol or substance abuse, and any physical illness that might affect cognitive function or produce hearing loss. Group characteristics are shown in Table 1. All subjects were right-handed as revealed by Edinburgh Handedness Inventory (Oldfield and Carolus, 1971). No difference was found in age or in gender composition between two subject groups ($P>0.05$).

Table 1
Demographic and clinical characteristics of schizophrenia patients and controls (means ± SD).

	Schizophrenia patients	Normal controls
Cases	19	25
Gender (male/female)	12/7	12/13
Age (years)	28.63 ± 12.33	32.88 ± 9.39
Age range	16–57	17–52
Onset age (years)	27.99 ± 12.57	
Illness duration (months)	7.68 ± 7.43	
PANSS		
Total score	62.0 ± 10.4	
Positive score	16.7 ± 5.8	
Negative score	16.2 ± 6.9	
General psychopathological score	29.1 ± 6.3	

PANSS: Positive and Negative Syndrome Scale.

2.2. ERP recording procedure

The EEG was acquired using a 64 channel quick-cap (Neuroscan), in which 60 scalp electrodes (FP1, F7, FP2, F3, FC3, FT7, T7, F8, F4, Fz, FCz, C3, TP7, FT8, FC4, Cz, CPz, CP3, P3, P7, T8, TP8, C4, P8, CP4, P4, Pz, Oz, O1, O2, FPz, AF3, AF7, F5, AF8, AF4, F1, FC5, F6, F2, FC1, C5, FC6, FC2, C2, C1, CP1, CP5, P5, PO7, PO8, C6, CP6, P6, CP2, PO4, P2, POz, P1, PO3) were positioned according to the international 10–10 system. The reference electrode was placed on the tip of nose. VEOG was obtained from two electrodes positioned above and below the left eye, and HEOG was obtained from two electrodes placed at the outer canthi of both eyes. The EEG was sampled continuously at a rate of 1000 Hz with a bandpass between 0.05 and 200 Hz. All impedances were kept below 10 kΩ.

Auditory ERPs were obtained using an oddball paradigm. Infrequent ($P=0.20$) target tones (1500 Hz, 80 dB SPL) were presented with frequent ($P=0.80$) standard tones (1000 Hz, 80 dB SPL). The tone duration was 50 ms with a rise and fall time of 10 ms. Auditory stimuli were delivered binaurally through headphones with variable inter-stimulus intervals ranging from 1.5 s to 2.5 s. There were 50 target tones and 200 non-target tones. Subjects were asked to press a button promptly and accurately in response to infrequent target tones. Averaging of ERP waves and related procedures was performed offline using Brain Vision Analyzer software (1.05, Brain Products Company, Germany).

Epoch length was 700 ms, including a 100-ms pre-stimulus baseline. EEG trials with incorrect responses were excluded. Ocular correction was done offline with the algorithm of Gratton and Coles (Gratton et al., 1983). For artifact rejection, trials were excluded if their voltage exceeded ±70 μV. The mean averaged EEG responses to target tones was 34.3 ± 6.7 trials for the patients, 37.2 ± 5.2 trials for the controls; the group difference was not significant ($F=2.64$, $P>0.05$).

2.3. Data analysis

Before peak identification, EEG was filtered with a 0.5 Hz high pass filter and with a 15 Hz low pass filter. Both P300 amplitude and P300 latency were measured at all 60 recording sites as the most positive voltage sampled in the latency range of 280~450 ms after the stimulus onset. N100 was measured from the ERPs to both target and non-target stimuli as the most negative peak between 50 and 150 ms at Fz.

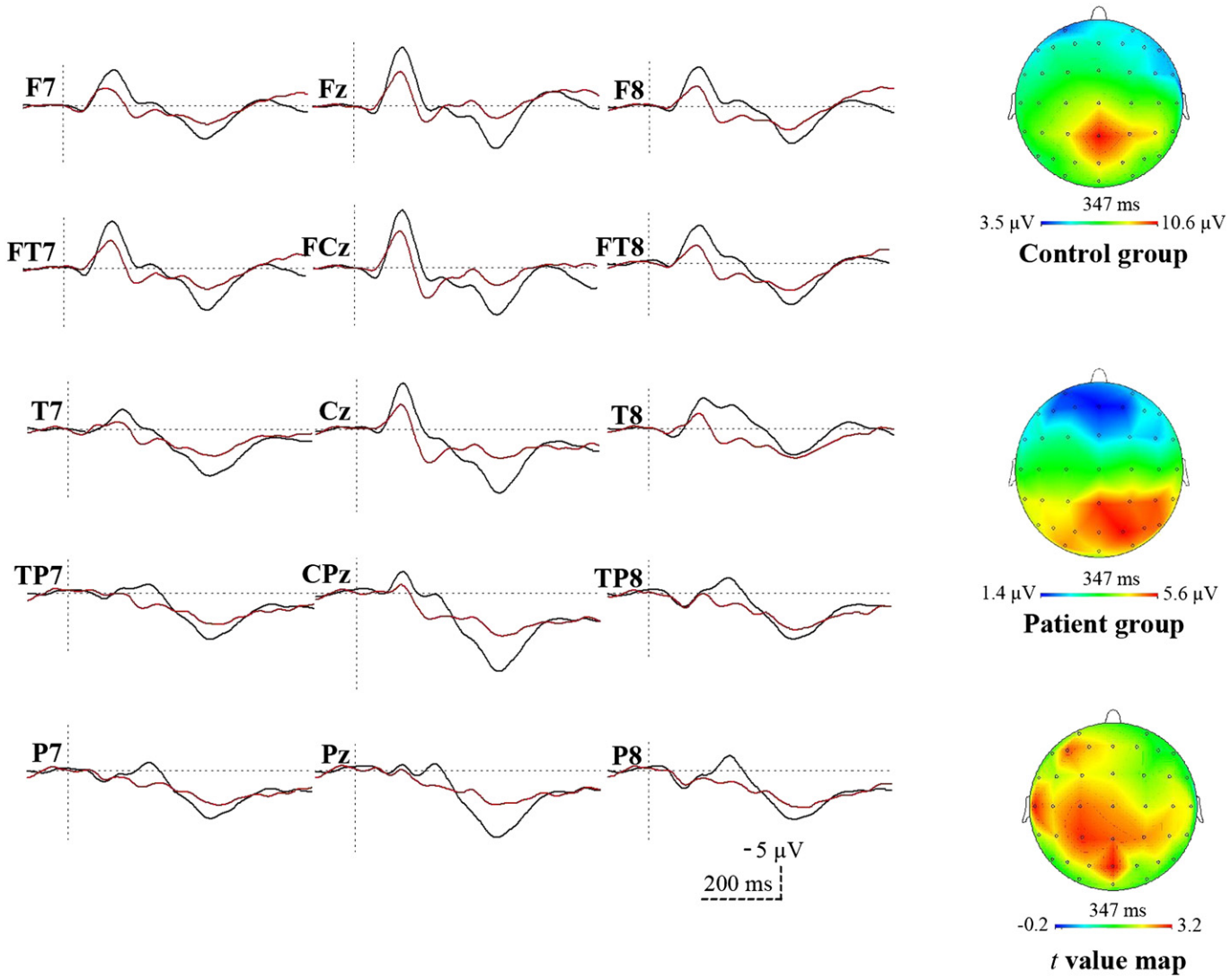

Fig. 1. The grand averaged ERP waveforms at F7, FT7, T7, TP7, P7, Fz, FCz, Cz, CPz, Pz, F8, FT8, T8, TP8 and P8, elicited by target stimuli. Black line, the control group; red line, patient group. Right side, the scalp distribution of P300 ERP at 347 ms after stimulus onset. The scalp topographic images demonstrated that P300 amplitude reduction among patients was predominantly over the left hemisphere.

The group and topographical differences in P300 amplitude and P300 latency were evaluated using a repeated measures analysis of variance (ANOVA). The between subject factor of the omnibus ANOVA was Group (2 levels: patients and controls). In order to explore the topographical P300 differences between patients and controls, the recording sites were integrated into 6 regions of interest (ROIs) including both the left-to-right hemispheric dimension (3 levels: left, medial and right, LMR) and the anterior–posterior dimension (2 levels: anterior and posterior, AP). For each ROI, 6 recording sites were included into the ANOVA as following: left-anterior (F7, F5, F3, FT7, FC5, FC3), left-posterior (TP7, CP5, CP3, P7, P5, P3), medial–anterior (F1, Fz, F2, FC1, FCz, FC2), medial–posterior (CP1, CPz, CP2, P1, Pz, P2), right-anterior (F8, F6, F4, FT8, FC6, FC4) and right-posterior (TP8, CP6, CP4, P8, P6, P4). Therefore, the overall ANOVA had three within-subject factors of LMR (3 levels: left, medial and right), AP (2 levels: anterior and posterior) and electrode (6 levels: 6 different recording sites). Any significant interaction of group × LMR, group × AP or group × LMR × AP were further parsed in two ways: first, by examining the effect of LMR, AP or LMR × AP in each participant group, and second, by examining the effect of Group for each level of LMR, AP or LMR × AP. When the Mauchly's sphericity assumption about the repeated measure factor was violated, the Greenhouse–Geisser correction of degrees of freedom was applied, with only the corrected probability values reported. Post hoc assessment of multiple comparisons employed Tukey's test.

LORETA images were obtained by estimating the current source density distribution for epochs of brain electric activity on a dense grid of 2394 voxels at 7-mm spatial resolution, which is established by Pascual-Marqui (1999) according to the digitized Talairach human brain altas (Pascual-Marqui, 1999). LORETA made use of the three-shell spherical head model registered to the Talairach atlas available as a digitized MRI from the Brain Imaging Centre, Montreal Neurologic Institute. Registration between spherical and realistic head geometry used EEG electrode coordinates reported by Towle et al. (1993). The solution space was restricted to cortical gray matter and the hippocampus, as determined by the corresponding digitized Probability Atlas, which is also available from the Brain Imaging Centre.

LORETA images were calculated for each subject using one digital bin of the peak P300 at Pz in the time frame 280 ~ 450 ms post-stimulus. The P300 LORETA images of the controls and of the patients were obtained by separately averaging individual P300 LORETA results for each group. The localization of the differences in P300 current source density between the two groups was assessed by voxel-by-voxel *t*-tests of the LORETA images of the log transformed computed current density power. In the resulting statistical three-dimensional images, cortical voxels that were significantly different were identified by a nonparametric approach using a randomization strategy (Nichols and Holmes, 2002) that determined the critical probability threshold values for the actual observed *t*-values with correction for multiple testing.

Relationships between P300 CSD values at voxels which show a group difference and psychopathological assessments were evaluated by performing Pearson's correlation test. If the voxels of group difference focus on some regions of interest (ROIs), exploratory correlational analyses will be performed for the mean P300 CSD values of all voxels within these ROIs and clinical measures. The significance level for all statistical tests was set at $P<0.05$ (two-tailed).

3. Results

3.1. Behavioral performance and ERP waveforms

The button press accuracy was 90.78% ± 4.11% among schizophrenia patients, and 98.79% ± 1.52% among normal controls. The mean reaction time was 711.7 ± 65.8 ms for the patients and 510.1 ± 126.4 ms for the controls. Overall, the patients responded less accurately ($F=81.0$, $P<0.001$) and more slowly ($F=39.9$, $P<0.001$) than the controls.

Fig. 1 shows ERP waveforms at F7, FT7, T7, TP7, P7, Fz, FCz, Cz, CPz, Pz, F8, FT8, T8, TP8 and P8, elicited by target stimuli. Visual inspection revealed that the P300 was remarkably smaller in the patients group than in the control group. The scalp topographic images demonstrated that P300 amplitude reduction among patients was predominantly over the left hemisphere.

3.2. Topographical comparison of P300 amplitude and P300 latency between patients and controls

The means of P300 amplitude and P300 latency at electrodes of ROIs are presented in Table 2. Overall, P300 amplitude was smaller for schizophrenia patients than for control subjects ($F=4.40$, $df=1,42$, $P=0.042$). The repeated measure ANOVA revealed a significant effect of LMR on P300 amplitude ($F=9.11$, $df=2,84$, $P=0.001$), suggesting a higher P300 amplitude over medial ROIs than over left or right ROIs. However, the factor of LMR demonstrated a significant interaction with group ($F=5.50$, $df=2,84$, $P=0.010$). Follow-up ANOVAs found that, the effect of LMR was only significant for the control group

Table 2
Mean (±SD) of P300 amplitude and P300 latency at electrodes of ROIs.

ROI	P300 amplitudes (μV)		P300 latency (ms)	
	Controls	Patients	Controls	Patients
Left-anterior				
F7	5.48 (5.83)	3.39 (4.80)	338.5 (32.0)	337.9 (40.7)
F5	6.09 (5.87)	3.31 (4.28)	339.9 (31.3)	333.1 (42.2)
F3	6.64 (5.63)	2.37 (3.97)	340.5 (27.2)	347.6 (37.2)
FT7	6.61 (6.14)	3.77 (4.31)	339.8 (29.0)	344.4 (40.0)
FC5	6.86 (5.82)	3.35 (4.44)	340.5 (30.0)	342.2 (41.3)
FC3	6.89 (4.92)	3.97 (4.52)	341.8 (29.1)	337.0 (38.4)
Left-posterior				
P7	7.60 (4.10)	5.73 (4.09)	352.6 (27.4)	347.3 (42.0)
P5	7.55 (4.08)	5.84 (4.02)	350.7 (29.7)	343.1 (41.1)
P3	7.85 (4.25)	5.53 (4.12)	346.6 (28.5)	342.7 (46.4)
TP7	7.27 (4.46)	5.30 (4.09)	351.3 (25.2)	346.8 (41.7)
CP5	7.78 (4.25)	5.52 (3.70)	349.6 (26.6)	347.6 (38.8)
CP3	9.08 (5.42)	5.90 (3.94)	348.5 (28.9)	341.6 (38.1)
Medial–anterior				
F1	6.63 (6.08)	2.54 (4.63)	337.2 (29.7)	339.7 (38.0)
Fz	6.62 (6.66)	2.65 (4.78)	337.8 (30.2)	341.2 (34.5)
F2	6.03 (6.25)	2.58 (4.57)	337.6 (30.1)	341.2 (34.4)
FC1	7.61 (6.20)	3.77 (4.60)	342.4 (30.9)	334.5 (38.4)
FCz	7.47 (6.26)	3.79 (5.27)	341.3 (32.4)	338.4 (38.8)
FC2	6.95 (5.97)	4.06 (4.76)	336.3 (30.1)	338.9 (36.0)
Medial–posterior				
P1	9.30 (4.71)	6.39 (3.93)	350.7 (29.1)	350.5 (38.8)
Pz	10.52 (5.50)	6.25 (3.90)	349.0 (29.8)	342.3 (41.4)
P2	10.01 (5.53)	7.35 (3.72)	350.2 (31.6)	349.8 (39.0)
CP1	9.88 (5.47)	5.82 (4.14)	347.9 (28.1)	343.3 (40.5)
CPz	11.89 (6.28)	7.25 (4.99)	344.2 (29.5)	343.2 (41.4)
CP2	10.81 (5.52)	6.83 (4.73)	350.0 (31.1)	342.2 (39.2)
Right-anterior				
F8	5.90 (5.22)	4.20 (5.82)	342.3 (30.8)	336.3 (38.9)
F6	5.71 (5.33)	3.85 (5.65)	342.3 (30.4)	338.6 (41.0)
F4	6.02 (5.74)	4.15 (6.42)	340.2 (28.2)	338.2 (40.4)
FT8	6.60 (4.46)	4.89 (5.05)	342.1 (29.5)	335.7 (37.8)
FC6	5.87 (5.21)	3.83 (3.76)	341.2 (31.1)	334.3 (36.0)
FC4	6.00 (4.41)	3.32 (3.22)	339.8 (28.9)	341.4 (32.7)
Right-posterior				
P8	8.25 (5.85)	6.08 (3.96)	351.9 (36.7)	351.7 (42.9)
P6	8.81 (5.35)	6.73 (4.25)	348.0 (34.7)	350.1 (40.1)
P4	8.81 (5.30)	5.59 (5.18)	350.3 (34.3)	352.2 (40.7)
TP8	7.23 (4.36)	5.92 (4.14)	348.4 (35.2)	349.6 (36.5)
CP6	8.77 (4.98)	6.01 (3.88)	352.8 (30.2)	355.2 (38.5)
CP4	10.46 (5.41)	6.95 (4.49)	350.4 (31.2)	342.0 (42.9)

($F=16.50$, $df=2,48$, $P<0.001$) but insignificant for the patient group ($F=1.53$, $df=2,36$, $P=0.233$), the effect of group was significant for left ROIs ($F=4.11$, $df=1,42$, $P=0.049$) and for medial ROIs ($F=6.09$, $df=1,42$, $P=0.018$), but insignificant for right ROIs ($F=2.73$, $df=1,42$, $P=0.106$). The overall ANOVA also detected a significant effect of AP on P300 amplitude ($F=35.90$, $df=1,42$, $P<0.001$), suggesting a higher P300 amplitude over posterior ROIs than over anterior ROIs. It showed no interaction with group ($F=0.01$, $df=1,42$, $P=0.937$). The interaction of LMR×AP was significant ($F=10.81$, $df=1,42$, $P<0.001$), suggesting a more remarkable effect of LMR on P300 amplitude over posterior ROIs than over anterior ROIs. However, its interaction with group was insignificant ($F=1.98$, $df=1,42$, $P=0.147$).

P300 latency showed no significant group difference between schizophrenia patients and normal controls ($F=0.06$, $df=1,42$, $P=0.812$). The effect of LMR on P300 latency was insignificant ($F=0.53$, $df=2,84$, $P=0.545$), and without any significant interaction with group ($F=0.02$, $df=2,84$, $P=0.953$). The effect of AP on P300 latency was significant ($F=5.58$, $df=1,42$, $P=0.023$), suggesting a longer P300 latency over posterior ROIs than over anterior ROIs, however, it showed no interaction with group ($F=0.05$, $df=1,42$, $P=0.818$). For P300 latency, neither the interaction of LMR×AP nor the interaction of group×LMR×AP was significant (for LMR×AP: $F=0.97$, $df=2,84$, $P=0.370$; for group×LMR×AP: $F=1.47$, $df=2,84$, $P=0.237$).

For the target ERPs at Fz, N100 amplitude was reduced significantly among patients (patients, -5.92 ± 3.60 μV, controls, -8.86 ± 4.20 μV; $F=5.97$, $df=1,42$, $P=0.019$), and N100 latency was shorter for schizophrenia patients than for controls (patients, 103.2 ± 11.3 ms, controls, 111.5 ± 4.7 ms; $F=11.23$, $df=1,42$, $P=0.002$). For the non-target ERPs at Fz, the reduction of N100 amplitude among schizophrenics was approaching a significant level (patients, -5.36 ± 3.33 μV, controls, -6.92 ± 2.69 μV; $F=2.97$, $df=1,42$, $P=0.092$), but no group difference was found for N100 latency (patients, 102.2 ± 11.9 ms, controls,106.6 ± 9.1 ms; $F=1.96$, $df=1,42$, $P=0.169$).

3.3. Comparisons between healthy controls and schizophrenia patients on LORETA images

Individual P300 current density was averaged for each group and the results are shown in Fig. 2. P300 current density in normal controls was symmetrically distributed over bilateral frontal lobes (medial frontal gyrus, paracentral lobule, superior frontal gyrus), bilateral parietal lobes (inferior parietal lobule, postcentral gyrus, precuneus, superior parietal lobule) and bilateral temporal lobes (superior temporal gyrus, middle temporal gyrus, inferior temporal gyrus and fusiform gyrus).

Schizophrenia patients showed P300 current density mainly over bilateral frontal lobe (medial frontal gyrus, middle frontal gyrus, paracentral lobule, superior frontal gyrus) and bilateral parietal lobes (inferior parietal lobule, postcentral gyrus, precuneus, superior parietal lobule). Unlike the control group, it was not very strong over the temporal lobes, specifically over the left temporal lobe. In

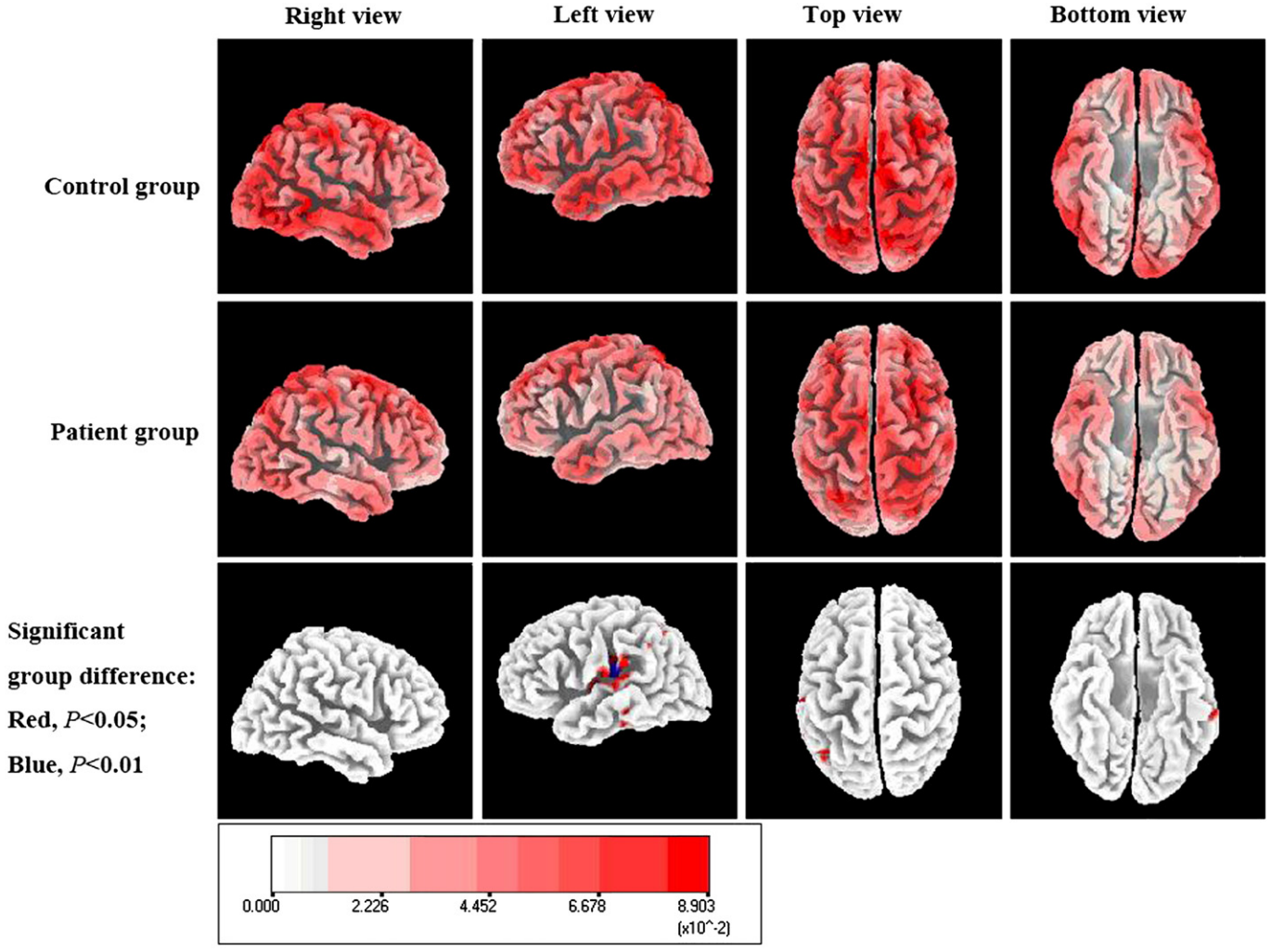

Fig. 2. The grand averaged LORETA images of P300 ERP and the maps showing the significant difference between the control group and the patient group.

Table 3
Voxels of LORETA values (means ± SD, 0.01 μA/mm^2) with a significant difference between patients and controls.

LORETA voxel					Control group	Patient group	t
ROI	BA	Talairach space					
Insula	13	−45	−23	21	1.72 ± 1.06	0.84 ± 0.85	−3.93[b]
	13	−38	−3	14	1.15 ± 0.82	0.53 ± 0.41	−3.63[b]
	13	−38	−11	1	1.61 ± 1.18	0.73 ± 0.56	−3.58[b]
	13	−31	−11	1	0.92 ± 0.67	0.42 ± 0.32	−3.57[b]
	13	−51	−30	22	3.31 ± 2.00	1.56 ± 1.57	−3.84[b]
	13	−38	−18	−4	1.05 ± 0.74	0.51 ± 0.41	−3.49[b]
	13	−38	−10	8	1.81 ± 1.26	0.88 ± 0.75	−3.48[b]
	13	−45	−10	8	2.31 ± 1.59	1.16 ± 1.09	−3.40[b]
	13	−31	−17	2	0.86 ± 0.60	0.42 ± 0.34	−3.38[b]
	13	−38	−4	8	2.02 ± 1.58	0.89 ± 0.67	−3.37[b]
Superior temporal gyrus	42	−65	−30	15	4.99 ± 3.79	1.97 ± 1.83	−3.99[b]
	29	−51	−30	15	3.30 ± 2.32	1.55 ± 1.54	−3.67[b]
	42	−58	−30	15	5.00 ± 3.67	2.11 ± 2.04	−3.89[b]
	42	−65	−24	15	5.71 ± 4.75	2.18 ± 1.56	−3.89[b]
	41	−51	−24	9	3.15 ± 2.49	1.54 ± 1.63	−3.55[b]
	22	−51	−10	8	3.20 ± 2.38	1.58 ± 1.64	−3.39[b]
	22	−65	−31	9	4.77 ± 4.29	2.23 ± 2.37	−3.37[b]
Middle temporal gyrus	21	−65	−32	−15	4.72 ± 3.86	1.94 ± 1.73	−3.67[b]
	21	−58	−32	−9	5.33 ± 4.22	2.32 ± 2.06	−3.43[b]
Transverse temporal gyrus	42	−58	−17	15	5.01 ± 4.08	1.99 ± 1.34	−3.65[b]
	41	−58	−24	9	4.95 ± 4.83	2.11 ± 2.32	−3.54[b]
Inferior temporal gyrus	20	−58	−32	−15	4.47 ± 3.64	1.70 ± 1.37	−4.00[b]
Postcentral gyrus	40	−58	−24	15	5.62 ± 4.51	2.13 ± 1.72	−4.18[a]
	40	−51	−23	21	3.31 ± 2.19	1.40 ± 1.29	−4.11[a]
	40	−51	−24	15	3.67 ± 2.67	1.60 ± 1.53	−4.07[a]
	43	−51	−17	15	2.72 ± 1.98	1.24 ± 1.13	−3.64[b]
Supramarginal gyrus	40	−58	−50	36	2.91 ± 2.21	1.28 ± 1.11	−3.64[b]
Superior parietal lobule	7	−38	−56	49	4.05 ± 2.09	2.28 ± 1.87	−3.43[b]
Inferior parietal lobule	40	−58	−30	22	5.57 ± 3.50	2.59 ± 2.35	−3.55[b]

[a] $P<0.01$.
[b] $P<0.05$.

Table 5
The correlations between LORETA values and the psychopathological assessments of schizophrenia patients.

ROI (number of voxels)	Positive factor		Negative factor		Total PANSS score	
	r	p	r	p	r	p
Left insula (40)	−0.109	0.657	−0.346	0.147	**−0.508**	**0.026**
Right insula (36)	0.059	0.811	0.049	0.843	0.03	0.902
Left STG (86)	−0.136	0.580	−0.348	0.144	**−0.554**	**0.014**
Right STG (96)	0.015	0.953	−0.07	0.777	−0.092	0.709
Left PCG (32)	−0.183	0.454	−0.316	0.187	**−0.562**	**0.012**
Right PCG (41)	−0.025	0.921	−0.066	0.790	−0.146	0.550

Bold number indicating $P<0.05$.

Fig. 2, both groups demonstrated a similar distribution of P300 current source density except in the left view, which clearly showed that P300 source activities over left STG and its nearby areas were reduced in the patients as compared to the controls.

Among 2394 voxels, the nonparametric approach of LORETA-key identified 29 voxels of significant group difference, whose t-values are above the critical probability threshold. Their Talairach spatial positions and the corresponding mean CSD values are given in Table 3. P300 CSD was reduced among schizophrenia patients at these voxels, which demonstrated a strong tendency for focusing on left insula, left superior temporal gyrus (STG) and left postcentral gyrus (PCG).

3.4. Correlations of LORETA values with psychopathological assessments

The correlation between the P300 CSD of schizophrenic patients at these 29 voxels and their psychopathological assessments has been shown in Table 4. There were 12 voxels, for which P300 CSD demonstrated a significant inverse correlation with patients' total PANSS scores. These voxels were mainly within left insula and left temporal cortex.

Table 4
Pearson's correlation coefficients (P values) of P300 CSD at voxels of a significant difference with patients' PANSS scores.

LORETA voxel					Total PANSS score	Positive factor score	Negative factor score
ROI	BA	Talairach space					
Insula	13	−45	−23	21	−0.37 (0.12)	−0.02 (0.93)	−0.32 (0.19)
	13	−38	−3	14	**−0.53 (0.02)**	−0.16 (0.53)	−0.29 (0.23)
	13	−38	−11	1	**−0.45 (0.05)**	−0.13 (0.59)	−0.27 (0.26)
	13	−31	−11	1	−0.42 (0.08)	−0.13 (0.59)	−0.24 (0.32)
	13	−51	−30	22	−0.39 (0.10)	−0.05 (0.84)	−0.29 (0.24)
	13	−38	−18	−4	−0.43 (0.07)	−0.13 (0.60)	−0.27 (0.27)
	13	−38	−10	8	**−0.52 (0.02)**	−0.15 (0.53)	−0.29 (0.23)
	13	−45	−10	8	**−0.56 (0.01)**	−0.15 (0.54)	−0.32 (0.18)
	13	−31	−17	2	−0.42 (0.07)	−0.14 (0.57)	−0.23 (0.34)
	13	−38	−4	8	**−0.52 (0.02)**	−0.15 (0.54)	−0.31 (0.20)
Superior temporal gyrus	42	−65	−30	15	−0.28 (0.25)	0.038 (0.88)	−0.27 (0.27)
	29	−51	−30	15	−0.39 (0.10)	−0.03 (0.91)	−0.31 (0.20)
	42	−58	−30	15	−0.33 (0.17)	0.00 (0.99)	−0.28 (0.24)
	42	−65	−24	15	−0.43 (0.07)	−0.08 (0.74)	−0.30 (0.22)
	41	−51	−24	9	**−0.47 (0.04)**	−0.03 (0.92)	−0.37 (0.12)
	22	−51	−10	8	**−0.57 (0.01)**	−0.15 (0.55)	−0.34 (0.16)
	22	−65	−31	9	**−0.49 (0.03)**	−0.03 (0.91)	−0.38 (0.11)
Middle temporal gyrus	21	−65	−32	−15	**−0.48 (0.04)**	−0.14 (0.57)	−0.27 (0.27)
	21	−58	−32	−9	**−0.48 (0.04)**	−0.14 (0.57)	−0.28 (0.26)
Transverse temporal gyrus	42	−58	−17	15	**−0.47 (0.04)**	−0.11 (0.65)	−0.29 (0.22)
	41	−58	−24	9	**−0.48 (0.04)**	−0.01 (0.98)	−0.39 (0.10)
Inferior temporal gyrus	20	−58	−32	−15	−0.21 (0.39)	−0.03 (0.89)	−0.16 (0.53)
Postcentral gyrus	40	−58	−24	15	−0.351(0.14)	−0.02 (0.94)	−0.30 (0.21)
	40	−51	−23	21	−0.34 (0.15)	−0.06 (0.82)	−0.26 (0.28)
	40	−51	−24	15	−0.39 (0.10)	−0.01 (0.98)	−0.34 (0.16)
	43	−51	−17	15	−0.43 (0.06)	−0.01 (0.98)	−0.37 (0.12)
Supramarginal gyrus	40	−58	−50	36	−0.38 (0.11)	−0.18 (0.47)	−0.22 (0.38)
Superior parietal lobule	7	−38	−56	49	−0.38 (0.11)	0.10 (0.69)	−0.44 (0.06)
Inferior parietal lobule	40	−58	−30	22	−0.43 (0.07)	−0.09 (0.71)	−0.28 (0.24)

Bold number indicating $P<0.05$.

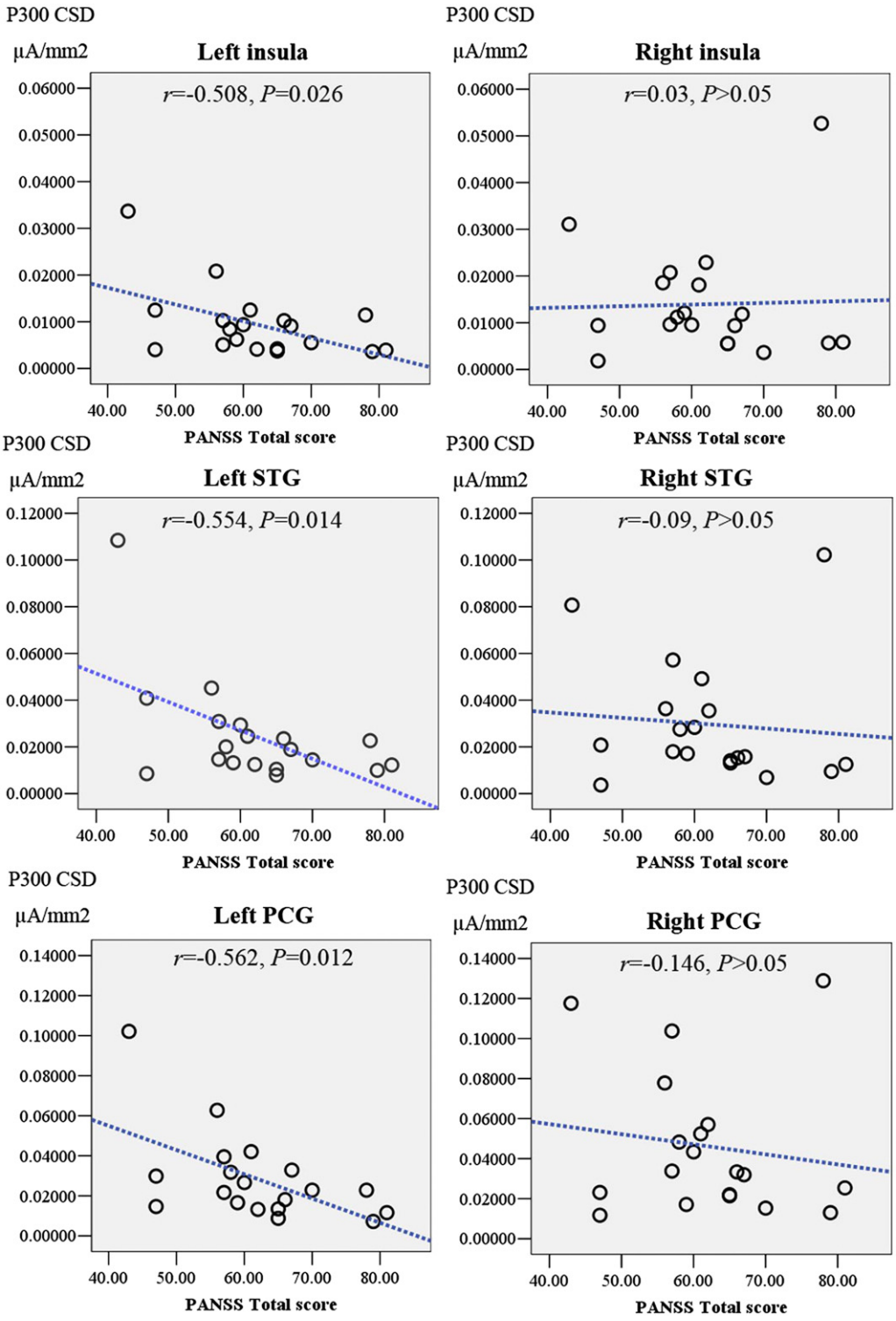

Fig. 3. Correlations between patients' P300 CSD over regions of interest and their total PANSS scores. CSD, current source density; STG, superior temporal gyrus; PCG, postcentral gyrus.

As the voxels showing the significant group difference were mainly in the left insula, the left STG and the left PCG, P300 CSD at voxels within these three areas were averaged and correlated with clinical measures. The correlation analyses were also performed for the homonymous regions within the right hemisphere, with the aim of left and right comparison. Results are shown in Table 5 and Fig. 3. An inverse correlation was found between P300 CSD values and the patients' total PANSS scores. However, the correlation was only significant for the left insula ($r=-0.508$, $P=0.026$), the left STG ($r=-0.554$, $P=0.014$) and the left PCG ($r=-0.562$, $P=0.012$); it was not significant for the right insula ($r=0.03$, $P=0.902$), the right STG ($r=-0.092$, $P=0.709$) and the right PCG ($r=-0.146$, $P=0.550$).

4. Discussion

In the present study, drug-naive first episode schizophrenia patients demonstrated a reduction in P300 amplitude with a normal P300 latency as compared to unaffected controls. They also showed a

smaller N100 amplitude and a shorter N100 latency in ERPs to target stimuli. These findings are in consistency with previous P300 studies of first episode schizophrenia (Brown et al., 2002; Demiralp et al., 2002; Wang et al., 2003a,b, 2005; van der Stelt et al., 2005; Renoult et al., 2007; Ozgürdal et al., 2008). The conventional topographical analysis revealed that P300 amplitude reduction in schizophrenics was significant over left and medial ROIs. LORETA analyses confirmed the main findings of topographical analysis, and further mapped the group differences of P300 to the left insula, left STG, and left PCG. For these regions, an inverse correlation between their mean P300 CSDs and the patients' total PANSS scores was significant, too.

The present study is the first LORETA study of auditory P300 in first episode schizophrenia. Furthermore, the high density recording in the present study made its findings more reliable, as compared to those using a low density recording (Michel et al., 2004). Kleinlogel et al. (2007) performed LORETA analysis of visual P300 elicited by CPT task among first episode patients using a low density recording. In comparison to the visual P300, the auditory P300 is a more robust and a more consistent abnormality among patients with schizophrenia in the literature (Duncan 1988).

LORETA analysis of P300 of controls revealed that the neural generators of scalp-recorded P300 were widespread over the cortex, including bilateral frontal, parietal and temporal lobes. This is consistent with the findings of previous studies using high density ERP recordings (for instance, Wang et al., 2003a). Compared with the control group, the voxels which showed a significantly reduced P300 current source density in the patient group were mainly over the left insula, left STG and left PCG, with a clear tendency to focus on the left STG and its nearby areas.

Although the reduced P300 current source density over the left STG has been reported among schizophrenia patients by previous studies (Kawasaki et al., 2007; Higuchi et al., 2008), the present study extended this finding to the drug-naive first episode patients. As the mean illness duration of our patients was about half a year, they were at the very early stage of schizophrenia. The functional changes within left STG probably are not an effect secondary to medication or to illness duration, and possibly reflected its significance in the pathogenesis of schizophrenia. This was further supported by the correlation between P300 CSD over the left STG and the patients' PANSS scores. Evidence of both structural and functional changes in the left STG has been well documented in first episode schizophrenia (McCarley et al., 2002; Kim et al., 2003; Takahashi et al., 2009). Progressive and dynamic disturbances in brain functional/structure have been suggested in schizophrenia from the prodomal phase to the full-blown of first episode of psychosis (Takahashi et al., 2009; Frommann et al., 2008). Frommann et al. (2008) reported that P300 amplitude reduction was very limited to a left temporoparietal site (TP7) among patients putatively in an early initial prodromal state (EIPS) for psychosis, but it was remarkably more spread to the sagittal midline electrodes among patients in a late initial prodromal state (LIPS). Similar findings were also made by Ozgürdal et al. (2008) and van der Stelt et al. (2005). However, what occurs in the left STG that eventually leads to the full-blown of first episode of psychosis remains an open and key question for future research.

In the present study, first episode schizophrenia patients also demonstrated a reduction in P300 current source density over left insula. Although this reduction has not been reported in previous P300-LORETA studies of schizophrenia, it is consistent with recent MRI studies, which applied voxel-based morphometric analysis of gray matter and revealed smaller bilateral insular cortex in first episode schizophrenia patients (Kubicki et al., 2002; Meisenzahl et al., 2008). In addition, a long prodromal phase was associated with smaller gray matter volumes in the left insular cortex (Lappin et al., 2007). The insular cortex is a paralimbic area of the brain thought to have important roles in sensory integration, auditory hallucinations and language. They are indeed activated when subjects perform an oddball task (Tarkka et al., 1996; Linden et al. 1999; Clark et al., 2000).

The present study also found reduced P300 current source density over the left postcentral gyrus in schizophrenia patients. Although it was a little different from the findings by Higuchi et al. (2008) who reported a reduced P300 current source density over the left precentral gyrus in schizophrenia patients, it was consistent with the MRI finding of significant decreases in gray matter within the left postcentral gyrus among first episode schizophrenia patients (Job et al., 2002).

In the present study, P300 CSD over left insula and left PCG was not only reduced among the schizophrenia patients, but also showed an inverse correlation with the patients' total PANSS scores, which likely highlights their significance in the pathogenesis of schizophrenia. However, as they have not been revealed by previous LORETA studies of chronic schizophrenia patients using either low density or high density ERP recording, future research must investigate whether these P300 abnormalities are state-related changes among first episode patients.

In the present study, the use of a button press to targets would cause response selection, preparation, and execution motor-related potentials to be active in the left hemisphere. This would elicit a concern about the effects of motor-related potentials (MRPs) on our findings. Since the patients were ~200 ms slower than controls, are the differences we observed really in P300 or just a reflection of the controls having left hemisphere MRP overlap with P300 that the patients do not? The MRPs precede the actual movement by several hundred milliseconds and include several components (Starr et al., 1995). The early MRPs, arising in supplementary motor cortex and premotor cortex, are not necessarily lateralized (Miller and Hackley, 1992). The later MRPs will probably distort the P300 field because they arise simultaneously with P300. Among the later MRPs, the lateralized readiness potential (LRP), a negative slope component, is largest over the contralateral motor area, beginning some 300 ms before and peaking approximately 100 ms or less before the movement (Miller and Ulrich, 1998). The LRP has been regarded as the greatest problem for P300 topography if the same hand is used to respond throughout the oddball task. The LRP possibly is associated with a reduction of P300 amplitude on button-pressing task comparing with silent counting task (Polich 1987; Salisbury et al., 2001). It is suggested that the MRPs could occlude difference in P300 topography between groups (Salisbury et al., 2001). Supposing the controls have left hemisphere MRP overlap with P300 and the patients do not in the present study, the melding of negative MRPs would cause P300 amplitude reduction among controls and the group difference in P300 over left hemisphere would be reduced rather than increased. Therefore, while the effects of MRPs on our findings cannot be excluded, the differences we observed in the present study are due to P300.

There are several limitations to the present study. First, the sample size was relatively small, and thus, the findings need to be replicated in a larger sample. Second, a cross-sectional design was applied. The P300 generator difference between first episode schizophrenia patients and controls must be confirmed in a prospective study that examines the effect of antipsychotics on P300 amplitude and P300 latency.

Acknowledgements

Funding for this study was provided by the National Natural Science Foundations of China (30770773), the National Scientific and Technological 863 Program of China (2008AA02Z412, 2007AA02Z420), the National Basic Research Program of China (973 Program, 2007CB512306), and the Youth Launching Program of Second Military University (06QN17). These grants had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

The authors kindly thank Mr. Weijun Su, who helped us in the EEG recording procedure.

References

Anderer, P., Pascual-Marqui, R.D., Semlitsch, H.V., Saletu, B., 1998. Electrical sources of P300 event-related brain potentials revealed by low resolution electromagnetic tomography. 1. Effects of normal aging. Neuropsychobiology 37, 20–27.

Brown, K.J., Gonsalvez, C.J., Harris, A.W., Williams, L.M., Gordon, E., 2002. Target and non-target ERP disturbances in first episode vs. chronic schizophrenia. Clin. Neurophysiol. 113, 1754–1763.

Clark, V.P., Fannon, S., Lai, S., Benson, R., Bauer, L., 2000. Responses to rare visual target and distractor stimuli using event-related fMRI. J. Neurophysiol. 83, 3133–3139.

Demiralp, T., Uçok, A., Devrim, M., Isoglu-Alkaç, U., Tecer, A., Polich, J., 2002. N2 and P3 components of event-related potential in first-episode schizophrenic patients: scalp topography, medication, and latency effects. Psychiatry Res. 111, 167–179.

Duncan, C.C., 1988. Event-related brain potentials: a window on information processing in schizophrenia. Schizophr. Bull. 14, 199–203.

Frommann, I., Brinkmeyer, J., Ruhrmann, S., Hack, E., Brockhaus-Dumke, A., Bechdolf, A., Wölwer, W., Klosterkötter, J., Maier, W., Wagner, M., 2008. Auditory P300 in individuals clinically at risk for psychosis. Int. J. Psychophysiol. 70, 192–205.

Goldstein, A., Spencer, K.M., Donchin, E., 2002. The influence of stimulus deviance and novelty on the P300 and novelty P3. Psychophysiology 39, 781–790.

Gratton, G., Coles, M.G., Donchin, E., 1983. A new method for off-line removal of ocular artifact. Electroencephalogr. Clin. Neurophysiol. 55, 468–484.

Halgren, E., Baudena, P., Clarke, J.M., Heit, G., Liégeois, C., Chauvel, P., Musolino, A., 1995a. Intracerebral potentials to rare target and distractor auditory and visual stimuli. I. Superior temporal plane and parietal lobe. Electroencephalogr. Clin. Neurophysiol. 95, 191–220.

Halgren, E., Baudena, P., Clarke, J.M., Heit, G., Marinkovic, K., Devaux, B., Vignal, J.P., Viraben, A., 1995b. Intracerebral potentials to rare target and distractor auditory and visual stimuli. II. Medial, lateral and posterior temporal lobe. Electroencephalogr. Clin. Neurophysiol. 95, 229–250.

Halgren, E., Marinkovic, K., Chauvel, P., 1998. Generators of the late cognitive potentials in auditory and visual oddball tasks. Electroencephalogr. Clin. Neurophysiol. 106, 156–164.

Higuchi, Y., Sumiyoshi, T., Kawasaki, Y., Matsui, M., Arai, H., Kurachi, M., 2008. Electrophysiological basis for the ability of olanzapine to improve verbal memory and functional outcome in patients with schizophrenia: a LORETA analysis of P300. Schizophr. Res. 101, 320–330.

Hirayasu, Y., Asato, N., Ohta, H., Hokama, H., Arakaki, H., Ogura, C., 1998. Abnormalities of auditory event-related potentials in schizophrenia prior to treatment. Biol. Psychiatry 43, 244–253.

Job, D.E., Whalley, H.C., McConnell, S., Glabus, M., Johnstone, E.C., Lawrie, S.M., 2002. Structural gray matter differences between first-episode schizophrenics and normal controls using voxel-based morphometry. Neuroimage 17, 880–889.

Katayama, J., Polich, J., 1998. Stimulus context determines P3a and P3b. Psychophysiology 35, 22–23.

Kawasaki, Y., Sumiyoshi, T., Higuchi, Y., Ito, T., Takeuchi, M., Kurachi, M., 2007. Voxel-based analysis of P300 electrophysiological topography associated with positive and negative symptoms of schizophrenia. Schizophr. Res. 94, 164–171.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13, 261–276.

Kim, J.J., Crespo-Facorro, B., Andreasen, N.C., O'Leary, D.S., Magnotta, V., Nopoulos, P., 2003. Morphology of the lateral superior temporal gyrus in neuroleptic naive patients with schizophrenia: relationship to symptoms. Schizophr. Res. 60, 173–181.

Kleinlogel, H., Strik, W., Begré, S., 2007. Increased NoGo-anteriorisation in first-episode schizophrenia patients during Continuous Performance Test. Clin. Neurophysiol. 118, 2683–2691.

Kubicki, M., Shenton, M.E., Salisbury, D.F., Hirayasu, Y., Kasai, K., Kikinis, R., Jolesz, F.A., McCarley, R.W., 2002. Voxel-based morphometric analysis of gray matter in first episode schizophrenia. Neuroimage 17, 1711–1719.

Lantz, G., Michel, C.M., Pascual-Marqui, R.D., Spinelli, L., Seeck, M., Seri, S., Landis, T., Rosen, I., 1997. Extracranial localization of intracranial interictal epileptiform activity using LORETA (low resolution electromagnetic tomography). Electroencephalogr. Clin. Neurophysiol. 102, 414–422.

Lappin, J.M., Dazzan, P., Morgan, K., Morgan, C., Chitnis, X., Suckling, J., Fearon, P., Jones, P.B., Leff, J., Murray, R.M., McGuire, P.K., 2007. Duration of prodromal phase and severity of volumetric abnormalities in first-episode psychosis. Br. J. Psychiatry Suppl. 51, s123–s127.

Linden, D.E., Prvulovic, D., Formisano, E., Völlinger, M., Zanella, F.E., Goebel, R., Dierks, T., 1999. The functional neuroanatomy of target detection: an fMRI study of visual and auditory oddball tasks. Cereb. Cortex 9, 815–823.

McCarley, R.W., Salisbury, D.F., Hirayasu, Y., Yurgelun-Todd, D.A., Tohen, M., Zarate, C., Kikinis, R., Jolesz, F.A., Shenton, M.E., 2002. Association between smaller left posterior superior temporal gyrus volume on magnetic resonance imaging and smaller left temporal P300 amplitude in first-episode schizophrenia. Arch. Gen. Psychiatry 59, 321–331.

Meisenzahl, E.M., Koutsouleris, N., Bottlender, R., Scheuerecker, J., Jäger, M., Teipel, S.J., Holzinger, S., Frodl, T., Preuss, U., Schmitt, G., Burgermeister, B., Reiser, M., Born, C., Möller, H.J., 2008. Structural brain alterations at different stages of schizophrenia: a voxel-based morphometric study. Schizophr. Res. 104, 44–60.

Michel, C.M., Murray, M.M., Lant, G., Gonzalez, S., Spinelli, L., Grave de Peralta, R., 2004. EEG source imaging. Clin. Neurophysiol. 115, 2195–2222.

Miller, J., Hackley, S.A., 1992. Electrophysiological evidence for temporal overlap among contingent mental processes. J. Exp. Psychol. Gen. 121, 195–209.

Miller, J., Ulrich, R., 1998. Locus of the effect of the number of alternative responses: evidence from the lateralized readiness potential. J. Exp. Psychol. Hum. Percept. Perform. 24, 1215–1231.

Mulert, C., Jager, L., Schmitt, R., Bussfeld, P., Pogarell, O., Moller, H.J., Juckel, G., Hegerl, U., 2004. Integration of fMRI and simultaneous EEG: towards a comprehensive understanding of localization and time-course of brain activity in target detection. Neuroimage 22, 83–94.

Nichols, T.E., Holmes, A.P., 2002. Nonparametric permutation tests for functional neuroimaging: a primer with examples. Hum. Brain Mapp. 15, 1–25.

Oldfield, R., Carolus, 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9, 97–113.

Ozgürdal, S., Gudlowski, Y., Witthaus, H., Kawohl, W., Uhl, I., Hauser, M., Gorynia, I., Gallinat, J., Heinze, M., Heinz, A., Juckel, G., 2008. Reduction of auditory event-related P300 amplitude in subjects with at-risk mental state for schizophrenia. Schizophr. Res. 105, 272–278.

Pae, J.S., Kwon, J.S., Youn, T., Park, H.J., Kim, M.S., Lee, B., Park, K.S., 2003. LORETA imaging of P300 in schizophrenia with individual MRI and 128-channel EEG. Neuroimage 20, 1552–1560.

Pascual-Marqui, R.D., 1999. Review of methods for solving the EEG inverse problem. Int. J. Bioelectromagn. 1, 75–86.

Pascual-Marqui, R.D., Michel, C.M., Lehmann, D., 1994. Low resolution electromagnetic tomography: a new method for localizing electrical activity in the brain. Int. J. Psychophysiol. 18, 49–65.

Polich, J., 1987. Response mode and P300 from auditory stimuli. Biol. Psychol. 25, 61–71.

Renoult, L., Prévost, M., Brodeur, M., Lionnet, C., Joober, R., Malla, A., Debruille, J.B., 2007. P300 asymmetry and positive symptom severity: a study in the early stage of a first episode of psychosis. Schizophr. Res. 93, 366–373.

Salisbury, D.F., Shenton, M.E., Sherwood, A.R., Fischer, I.A., Yurgelun-Todd, D.A., Tohen, M., McCarley, R.W., 1998. First-episode schizophrenic psychosis differs from first-episode affective psychosis and controls in P300 amplitude over left temporal lobe. Arch. Gen. Psychiatry 55, 173–180.

Salisbury, D.F., Rutherford, B., Shenton, M.E., McCarley, R.W., 2001. Button-pressing affects P300 amplitude and scalp topography. Clin. Neurophysiol. 112, 1676–1684.

Soltani, M., Knight, R.T., 2000. Neural origins of the P300. Crit. Rev. Neurobiol. 14, 199–224.

Starr, A., Sandroni, P., Michalewski, H.J., 1995. Readiness to respond in a target detection task: pre- and post-stimulus event-related potentials in normal subjects. Electroencephalogr. Clin. Neurophysiol. 96, 76–92.

Stevens, M.C., Laurens, K.R., Liddle, P.F., Kiehl, K.A., 2006. The hemodynamics of oddball processing during single-tone and two-tone target detection tasks. Int. J. Psychophysiol. 60, 292–303.

Strik, W.K., Fallgatter, A.J., Brandeis, D., Pascual-Marqui, R.D., 1998. Three-dimensional tomography of event-related potentials during response inhibition: evidence for phasic frontal lobe activation. Electroencephalogr. Clin. Neurophysiol. 108, 406–413.

Sumiyoshi, T., Higuchi, Y., Kawasaki, Y., Matsui, M., Kato, K., Yuuki, H., Arai, H., Kurachi, M., 2006. Electrical brain activity and response to olanzapine in schizophrenia: a study with LORETA images of P300. Prog. Neuropsychopharmacol. Biol. Psychiatry 30, 1299–1303.

Takahashi, T., Wood, S.J., Yung, A.R., Soulsby, B., McGorry, P.D., Suzuki, M., Kawasaki, Y., Phillips, L.J., Velakoulis, D., Pantelis, C., 2009. Progressive gray matter reduction of the superior temporal gyrus during transition to psychosis. Arch. Gen. Psychiatry 66, 366–376.

Tarkka, I.M., Micheloyannis, S., Stokić, D.S., 1996. Generators for human P300 elicited by somatosensory stimuli using multiple dipole source analysis. Neuroscience 75, 275–287.

Towle, V.L., Bolanos, J., Suarez, D., Tan, K., Grzeszczuk, R., Levin, D.N., Cakmur, R., Frank, S.A., Spire, J.P., 1993. The spatial location of EEG electrodes: locating the best-fitting sphere relative to cortical anatomy. Electroencephalogr. Clin. Neurophysiol. 86, 1–6.

van der Stelt, O., Lieberman, J.A., Belger, A., 2005. Auditory P300 in high-risk, recent-onset and chronic schizophrenia. Schizophr. Res. 77, 309–320.

Volpe, U., Mucci, A., Bucci, P., Merlotti, E., Galderisi, S., Maj, M., 2007. The cortical generators of P3a and P3b: a LORETA study. Brain Res. Bull. 73, 220–230.

Wang, J., Hiramatsu, K., Hokama, H., Miyazato, H., Ogura, C., 2003a. Abnormalities of auditory P300 cortical current density in patients with schizophrenia using high density recording. Int. J. Psychophysiol. 47, 243–253.

Wang, J., Hirayasu, Y., Hiramatsu, K., Hokama, H., Miyazato, H., Ogura, C., 2003b. Increased rate of P300 latency prolongation with age in drug-naive first episode schizophrenia. Clin. Neurophysiol. 114, 2029–2035.

Wang, J., Hirayasu, Y., Hokama, H., Tanaka, S., Kondo, T., Zhang, M., Xiao, Z., 2005. Influence of duration of untreated psychosis on auditory P300 in drug-naive and first-episode schizophrenia. Psychiatry Clin. Neurosci. 59, 209–214.

Winterer, G., Mulert, C., Mientus, S., Gallinat, J., Schlattmann, P., Dorn, H., Herrmann, W.M., 2001. P300 and LORETA: comparison of normal subjects and schizophrenic patients. Brain Topogr. 13, 299–313.

Worrell, G.A., Lagerlund, T.D., Sharbrough, F.W., Brinkmann, B.H., Busacker, N.E., Cicora, K.M., O'Brien, T.J., 2000. Localization of the epileptic focus by low-resolution electromagnetic tomography in patients with a lesion demonstrated by MRI. Brain Topogr. 12, 273–282.