Progress in Neuro-Psychopharmacology & Biological Psychiatry 35 (2011) 1908–1917

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

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

Source imaging of P300 auditory evoked potentials and clinical correlations in patients with posttraumatic stress disorder

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ARTICLE INFO

Article history:
Received 26 April 2011
Received in revised form 1 August 2011
Accepted 2 August 2011
Available online 6 August 2011

Keywords:
Current source density
P300
Posttraumatic stress disorder
sLORETA

ABSTRACT

Objective: Posttraumatic stress disorder (PTSD) is associated with abnormal information processing. The P300 component of event-related potentials (ERPs) is known to be a useful marker of information processing. The purposes of this study were to determine the P300 current source density in PTSD patients, and its relationship with symptom severity.

Methods: ERPs were recorded in 30 PTSD patients and 33 healthy controls while participants were performing the auditory oddball task. We compared P300 current source density data – obtained by standardized low-resolution brain electromagnetic tomography (sLORETA) – between the two groups. The correlation between P300 current source density and clinical symptoms (as evaluated using the Korean version of the Structured Interview for PTSD — K-SIPS and Davidson Trauma Scale — K-DTS) was conducted.

Results: In PTSD patients, the current source density of P300 is significantly reduced in the inferior frontal gyrus, precentral gyrus, insula, and anterior cingulate compared to healthy controls. Total K-DTS scores were correlated with the P300 current source density in the posterior cingulate gyrus. The K-SIP B items (re-experiencing) and K-SIB D items (increased arousal) were positively correlated with P300 current source densities in several brain regions located in the frontal, parietal, and temporal lobe ($p<0.05$). Conversely, the K-SIP C items (avoidance and numbing) were negatively correlated with P300 current source densities in the superior and middle frontal gyri in the frontal lobes ($p<0.05$).

Conclusion: The P300 current source densities reflected the pathophysiology of PTSD patients. PTSD symptoms were related to different neural activities, depending on their symptom characteristics.

1. Introduction

Posttraumatic stress disorder (PTSD) is a prevalent and life-disturbing disorder. Previous studies have found that the lifetime prevalence rate of PTSD ranges from 5% to 10%, and that the 12-month prevalence rate is about 2–5% (Alonso et al., 2004a, b, c; Kessler et al., 2005; Wittchen and Jacobi, 2005). PTSD is associated with various problems, including impairments of social interaction (Amaya-Jackson et al., 1999; Norman et al., 2007; Stein et al., 1997). The amount of work impairment associated with PTSD is comparable to the amount of work impairment associated with major depressive disorder (Lim et al., 2000).

PTSD is unique among psychiatric disorders, in that exposure to a traumatic event always plays a part in the etiology of PTSD, but not all people who experience trauma get PTSD. People may develop PTSD after experiencing traumatic events such as traffic accidents, rape, natural disasters, military combat, or physical illness (Zohar et al., 2008). According to Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria, PTSD is characterized by the presence of three symptom clusters: reexperiencing (criterion B), avoidance and numbing (criterion C), and increased arousal (criterion D) (APA, 1994). Many patients with PTSD have reexperiencing symptoms including flashbacks, distressing memories, and nightmares. Also, they usually attempt to avoid activities and thoughts related to the trauma, and frequently show a markedly decreased capacity to experience pleasure. They often show blunted affect and a feeling of detachment from others. In addition, increased arousal may be related

Abbreviations: PTSD, posttraumatic stress disorder; ERP, event-related potential; sLORETA, standardized low-resolution brain electromagnetic tomography; K-SIPS, Korean version of the Structured Interview for PTSD; K-DTS, Korean version of Davidson Trauma Scale; SCID, Structured Clinical Interview for DSM; MMPI, Minnesota Multiphasic Personality Inventory; SSRIs, selective serotonin reuptake inhibitors; BDI, Beck Depression Inventory; HAMD-17, 17-item Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale.

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doi:10.1016/j.pnpbp.2011.08.002

to sleep disturbance, the startle response, and irritability which are often experienced by patients with PTSD (Vieweg et al., 2006).

Currently, PTSD is classified as an anxiety disorder in the DSM diagnostic system. However, the current diagnostic criteria of PTSD (APA, 1994) include specific disturbances that are different from other anxiety disorders such as disturbances of cognition and memory including intrusive memories (criterion B-1), inability to recall an important aspect of the trauma (criterion C-3), and concentration difficulty (criterion D-3). Furthermore, numerous previous studies have suggested that PTSD is associated with altered information processing such as disturbances in working memory and attention and difficulty in encoding information and inhibiting distracting stimuli (Vasterling et al., 1998, 2002). Working memory is known to depend on networks that include various frontal and parietal cortical regions and subcortical structures, and attention is mediated by the posterior parietal, prefrontal, and limbic networks (Behrmann et al., 2004; Budson, 2009; Rossi et al., 2009). It has been reported that the inferior frontal cortex, medial temporal cortex, and cerebellum are involved in episodic memory (Achim and Lepage, 2005; Cabeza and Nyberg, 2000). These results suggest that alternations in a wide range of neural processes may be involved in the pathophysiology of PTSD.

In a functional magnetic resonance imaging (fMRI) study, blood oxygen-level-dependent (BOLD) activity was greater in the ventral-limbic regions and altered dorsal-attention and anterior cingulate function were observed in response to threatening stimuli in patients with PTSD (Pannu Hayes et al., 2009). Another fMRI study reported that patients with PTSD exhibited enhanced BOLD activity in the rostral and dorsal anterior cingulate cortex, left amygdala, and posterior parietal networks in response to nonthreatening stimuli, which may reflect generalized hypervigilance (Bryant et al., 2005).

Until now, a number of previous studies have focused on the relationship between PTSD and the hippocampus that is believed to play an important role in cognitive functions such as learning, memory, and stress regulation. A study of meta-analysis suggested that the change of hippocampal volume is associated with PTSD symptom severity (Karl et al. 2006b). The same study also reported that PTSD is associated with abnormalities in multiple fontal-limbic system structures such as the amygdala, the anterior cingulate cortex and prefrontal cortical regions (Karl et al. 2006b). This finding is consistent with the results of previous functional neuroimaging research in patients with PTSD (Bremner et al., 1999, 2003, 2004; Clark et al., 2003; Matsuo et al., 2003; Rauch et al., 1996; Shin et al., 1999, 2001, 2004).

Event-related potentials (ERPs) are considered to be a useful tool to evaluate information processing in PTSD with high temporal resolution (Karl et al., 2006a). A recent study employed meta-analytic procedures of ERPs in patients with PTSD found that patients with PTSD exhibited a reduction of the P50 suppression response and a reducing or an augmenting response on the P200 component (Karl et al., 2006a). Reduced P50 suppression has been hypothesized to indicate disturbances in filtering sensory stimuli due to the impairment of central inhibitory processes, and the P200 augmenting–reducing response may reflect the alteration of functional levels of the serotonergic system (Hegerl and Juckel, 1993; White and Yee, 1997). These findings therefore suggest that PTSD is associated with disturbance to attention and anxiety modulation as well as depressive mood. Other studies have found that the P300 amplitude in response to target oddball stimuli is reduced in PTSD patients relative to normal controls (McFarlane et al., 1993; Metzger et al., 1997). It is well known that a reduced P300 amplitude may be interpreted as an index of general cognitive impairments and disturbance of attention (Polich, 1998; Portin et al., 2000).

The source localization method has been used to evaluate the pathophysiology of various mental illnesses. The current source densities of specific ERP components were demonstrated to be useful biomarkers of mental illness (Wang et al., 2010; Winterer et al., 2001). Low-resolution electromagnetic tomography (LORETA) provides three-dimensional images of brain electrical activity (Pascual-Marqui et al., 1999). LORETA current source imaging is known to provide good estimates of the locations of activated brain regions (Mulert et al., 2004). With high temporal resolution, LORETA has been broadly applied to investigate neural activities in psychiatric disorders (Saletu et al., 2002). Standardized LORETA (sLORETA) has recently been introduced, whereby localization inference is based on images of standardized current density (Fuchs et al., 2002; Jurcak et al., 2007; Pascual-Marqui, 2002). However, to our knowledge, there have been no studies investigating the differences in ERP current source density between normal controls and PTSD patients, and the relationships between the ERPs current source density and the symptom severity in PTSD.

Previous studies on P300-related sources have found that the main activity is observed in brain regions such as the frontal lobe, medial and lateral temporal lobe planes, posterior cingulum, inferior parietal lobe and neighboring posterior superior temporal plane, intraparietal sulcus, and the surrounding superior parietal sulcus (Moores et al., 2003; Park et al., 2003; Winterer et al., 2001). However, it has been suggested that P300-related sources may differ depending on the experimental paradigm, subjects, and time frame. Thus, it appears that investigating all brain regions associated with differences in the P300 current source density may be more useful than comparing the P300 current source densities of predetermined regions of interest (Moores et al., 2003; Park et al., 2003; Winterer et al., 2001).

To the best of our knowledge, the present study is the first to investigate the pattern of P300 source imaging in PTSD. We hypothesized that PTSD patients would exhibit abnormal patterns of P300 in response to nonthreatening stimuli, and that the current source density of P300 would reflect brain regions associated with the pathophysiology of PTSD. Furthermore, we aimed to examine the correlation between symptom severity and P300 current source density in PTSD patients.

2. Methods

2.1. Subjects

The participants comprised 33 healthy controls (13 females, 20 males; age, 32.4 ± 11.6 years) and 30 patients with PTSD (14 females, 16 males; age, 38.3 ± 14.5 years, mean ± SD) who were recruited from the Psychiatry Department of Inje University Ilsan Paik Hospital. All of the PTSD patients developed PTSD after experiencing motor vehicle accidents and were diagnosed using the Structured Clinical Interview for DSM, 4th edition (SCID) Axis I Psychiatric Disorders (APA, 1994; Frist et al., 1996). Out of 30 patients with PTSD, 28 patients were taking antidepressants: 17 were taking selective serotonin reuptake inhibitors (SSRIs), five venlafaxine, three mirtazapine, two duloxetine and one bupropion. Twenty nine patients were taking benzodiazepine: 13 were taking lorazepam, 12 clonazepam, 2 alprazolam and 2 diazepam.

Normal controls were recruited from the local community through local newspapers and posters. During screening, they were evaluated with the SCID Axis I Psychiatric Disorders (APA, 1994; Frist et al., 1996) and received physical examination. They also completed the Minnesota Multiphasic Personality Inventory (MMPI: Kim, 1996). Only those with the normal range of the MMPI scores were included in the study. Exclusion criteria included the presence of any identifiable psychiatric or neurological disorder, hearing impairment, head injury, any personal history of psychiatric disease, a family history of psychiatric illness, mental retardation, alcohol or substance abuse, and physical illness that can affect cognitive function or cause hearing loss. All participants were right-handed, as determined by asking which hand they tended to use for writing and other precise motor skills and did not have hearing impairment on the 512-Hz tuning fork test. After being instructed to the details of the study, all of the subjects gave written informed consent to participate. This study was approved by the Ethics Committee of Inje University Ilsan Paik Hospital. The demographics of the two groups are

Table 1
Demographic and clinical characteristics of the patients with PTSD and normal controls.

	PTSD ($n=30$)		Normal controls ($n=33$)		p
	Mean	SD	Mean	SD	
Age (years)	38.33	14.48	32.39	11.63	0.08
Sex (male:female)	16:14		20:13		0.74
Education (years)	12.4	2.34	13.23	2.92	0.23
K-DTS	85.3	19.33			
K-SIP	41.67	9.4			
BDI	29.4	12.4			
HAMD-17	21.1	8.52			
HAMA	24.93	8.56			

Note: PTSD, posttraumatic stress disorder; DTS, Davidson Trauma Scale; SIP, Structured Interview for PTSD; BDI, Beck Depression Inventory; HAMD-17, 17-item Hamilton Depression Rating Scale; HAMA, Hamilton Anxiety Rating Scale.

given in Table 1; there were no significant group differences with regard to gender distribution, age, or education.

2.2. Clinical symptom assessment

The Davidson Trauma Scale (DTS) and Structured Interview for PTSD (SIP) were administered to patients with PTSD. DTS and SIP have been standardized for Korean population (Kim et al., 2009; Seo et al., 2008). The DTS is a self-reported measure that reflects the frequency and severity of PTSD symptoms and has been demonstrated to be sensitive to the treatment effects of selective serotonin reuptake inhibitors (SSRIs) in patients with PTSD symptoms (Davidson et al., 2002). The DTS is a 17-item self-reported questionnaire on a 5-point Likert-type scale that scores the severity and frequency of PTSD symptoms. The DTS is easy to administer and takes less than 10 min. The DTS has been administered in a variety of populations, including men and women with different traumata. The Korean version of DTS (K-DTS; Seo et al., 2008) has shown good internal consistency (Cronbach $\alpha=0.97$) and test–retest reliability ($r=0.93$). The SIP scale (Davidson et al., 1997) comprises 17 items that reflect the DSM-IV criteria for PTSD: re-experiencing (5 items), avoidance and numbing (7 items), and increased arousal (5 items). Each item is rated on a scale of 0–4. The Korean version of SIP (K-SIP; Kim et al., 2009) has shown good internal consistency (Cronbach $\alpha=0.92$) and test–retest reliability ($r=0.87$).

Comorbid depressive and anxiety symptoms in patients with PTSD were evaluated using the Beck Depression Inventory (BDI; Beck et al., 1961), 17-item Hamilton Depression Scale (HAMD-17: Hamilton, 1960), and Hamilton Anxiety Scale (HAMA; Hamilton, 1959).

All interview and assessment of PTSD patients were conducted by an experienced psychiatrist (Lee S.H.).

2.3. ERP recording and analysis

The subjects were seated in a comfortable chair in a sound-attenuated room. Stimulus presentation and data synchronization with the electroencephalogram (EEG) were accomplished with E-Prime (Psychology Software Tools, Pittsburgh, PA, USA). The auditory oddball paradigm was used as a stimulation protocol. Infrequent target tones of 1500 Hz were presented randomly with frequent standard tones of 1000 Hz. The probabilities of standard tones and target tones were 85% and 15%, respectively. In total, 400 auditory stimuli were presented; the tone duration was 100 ms, with rise and fall times of 10 ms, and the interstimulus interval was 1500 ms. An experimental block consisted of 400 stimuli preceded by a practice block of 20 stimuli. These auditory stimuli were delivered via MDR-D777 headphones (Sony, Tokyo, Japan) at 85 dB SPL. The subjects were asked to press a button promptly in response to target tones.

EEG activity was recorded using a NeuroScan SynAmps amplifier (Compumedics USA, El Paso, TX, USA) and Ag–AgCl electrodes mounted in a Quick Cap using a modified 10–20 placement scheme. A total of 62 scalp electrodes (FP1, FPZ, FP2, AF3, AF4, F7, F5, F3, F1, FZ, F2, F4, F6, F8, FT7, FC5, FC3, FC1, FCZ, FC2, FC4, FC6, FT8, T7, C5, C3, C1, CZ, C2, C4, C6, T8, TP7, CP5, CP3, CP1, CPZ, CP2, CP4, CP6, TP8, P7, P5, P3, P1, PZ, P2, P4, P6, P8, PO7, PO5, PO3, POZ, PO4, PO6, PO8, CB1, O1, OZ, O2, and CB2) were used in this study. The vertical electrooculogram (EOG) was recorded using two electrodes, one located above and one below the right eye. The horizontal EOG was recorded at the outer canthus of each eye. EEG data were recorded with a 1- to 100-Hz band-pass filter at a sampling rate of 1000 Hz. The ground electrode was placed on the forehead and the reference electrodes were located at both mastoids. The electrode impedance was less than 5 kΩ. Averaging of the ERP waves and related procedures were performed using NeuroScan 4.3 software (Compumedics USA). Gross movement artifacts were removed from the recorded data by visual inspection, and eye blinks were removed using established mathematical procedures (Semlitsch et al., 1986). Trials were rejected if they included significant physiological artifacts (amplitude exceeding ± 75 μV) at all cortical electrode sites. After artifact removal, baseline correction was conducted by subtracting the mean value for 100 ms before stimulus onset from the poststimulus data for each trial. Data were band-pass filtered at 1–30 Hz and then epoched to 100 ms prestimulus and 900 ms poststimulus. For the reference, P300 peak amplitudes and latencies were measured from the most-positive peak between 300 and 450 ms for the target tones at Fz, Cz, and Pz. The numbers of accepted epochs in the PTSD and normal control groups were 49.5 ± 8.0 and 51.7 ± 7.0, respectively. The averaged acceptance rate did not differ significantly between the two groups ($p=0.25$).

2.4. Source localization of the P300 activity using sLORETA

Current source analysis of the P300 component was performed using sLORETA software (Pascual-Marqui, 2002), which calculates a particular solution of the nonunique EEG inverse problem based on the assumption of maximum synchronization between neighboring voxels (Fuchs et al., 2002; Jurcak et al., 2007). sLORETA images were obtained by estimating the current source density distribution on a dense grid of 6239 voxels with a 5-mm intervoxel distance located in cortical gray matter and hippocampus (Pascual-Marqui et al., 1999). The lead-field matrix was calculated by applying the boundary element method to a three-layer realistic head model extracted from the MNI152 template provided by the Brain Imaging Center, Montreal Neurological Institute (Fuchs et al., 2002; Jurcak et al., 2007). The solution space was restricted to the cortical gray matter and hippocampus. sLORETA images for each ERP were calculated for infrequent target tones in the time frame from 300 to 450 ms poststimulus. We used the data from all 62 electrodes for source localization analysis.

2.5. Statistical analysis

Independent t-test was used to investigate the individual demographic and clinical variables between two PTSD and normal controls. Analysis of covariance (ANCOVA) was used for between-groups comparison when some variables are needed to be controlled.

The current source density of the ERP waveform was computed for each subject using a statistical nonparametric mapping method that was provided by the sLORETA software (Pascual-Marqui, 2002). Differences in the P300 current source density between patients with PTSD and healthy controls were assessed using voxel-by-voxel comparison with independent t-test for 6239 voxels, followed by adjustments for multiple comparisons. In order to evaluate the relationship between symptom scores and current source density, the correlation between clinical scales and the P300 current source density of each voxel on

sLORETA images was assessed using the Pearson correlation test. To eliminate false-positive relationships between symptom scores and voxel activations in such large comparison, we employed permutation testing to assess whether the correlation value of each voxel was greater than that occurred by chance (Coutanche et al., 2011; Vul et al., 2009). For each individual voxel, we permuted the clinical scores 10,000 times independently to generate a null distribution of correlation coefficients and tested whether the original correlation coefficient exceeded the statistical significance of $p<0.05$ or not. As a result, we visualized the distribution of correlation coefficients which was significant after the permutation test on the standard MR brain image.

3. Results

3.1. Demographic and clinical data

The characteristics of the subjects in the two groups are given in Table 1. The DTS and SIP scores in the PTSD group were 85.3 ± 19.3 and 41.7 ± 9.4, respectively, and the BDI, HAMA, and HAMD-17 scores were 29.4 ± 12.4, 24.9 ± 8.6, and 21.1 ± 8.5, respectively.

3.2. Behavioral results

Compared to the healthy controls, the PTSD patients had a significantly lower hit rate ($77.9 \pm 25.2\%$ vs. $97.1 \pm 4.4\%$; $t=4.129$, $p<0.001$) and slower reaction times (563 ± 120 ms vs. 463 ± 87 ms; $t=-3.844$, $p<0.001$) to the target. The rate of false alarms did not differ significantly between the two groups ($6.8 \pm 18.3\%$ vs. $0.4 \pm 0.5\%$; $t=-1.914$, $p=0.07$).

3.3. P300 amplitude analysis

PTSD patients exhibited a significantly reduced P300 amplitude relative to the normal controls at Fz (5.57 ± 3.01 vs. 8.43 ± 3.35 μV, $p=0.002$), Cz (5.44 ± 2.79 vs. 8.78 ± 3.48 μV, $p<0.001$), and Pz (4.97 ± 2.69 vs. 7.72 ± 2.67 μV, $p<0.001$) after adjustment for age. However, the P300 latency did not differ significantly between the PTSD group and the normal controls at Fz (357 ± 23 vs. 357 ± 20 ms, $p=0.835$), Cz (362 ± 33 vs. 352 ± 23 ms, $p=0.304$), or Pz (368 ± 36 vs. 354 ± 24 ms, $p=0.154$) after adjustment for age.

3.4. sLORETA images of normal controls and PTSD patients

Grand average waveforms at the Fz, Cz, and Pz electrodes of PTSD patients and normal controls are shown in Fig. 1. Statistical comparisons revealed significant differences in the P300 current source density between the two groups. sLORETA analysis revealed that the current source densities in frontal lobe regions such as the inferior frontal gyrus [Brodmann's area (BA) 9] and precentral gyrus (BA 6), insula (BA 13), and in limbic lobe regions such as the anterior cingulate gyrus (BA 33) were significantly lower in the PTSD group than in healthy controls ($p<0.05$; Fig. 2, Table 2).

3.5. Correlations of sLORETA current source density with symptom severity

Fig. 3 demonstrates the correlation between the P300 current source density of PTSD patients and their K-DTS scores. A significant inverse correlation ($r=-0.44$, $p<0.05$) was noted between K-DTS scores and the P300 current source density only in the posterior cingulate gyrus (BA 30; MNI coordinates $X=25$, $Y=-70$, $Z=+10$; Talairach coordinates $X=+25$, $Y=-67$, $Z=13$).

The correlations between the P300 current source density of patients with PTSD and their K-SIP scores, relative to symptom clusters, are presented in Fig. 4 and Table 3. In terms of the reexperiencing items, there was a significant positive correlation ($p<0.05$) between the P300 current source density and their total scores in several parietal regions such as the inferior (BA 40, $r=0.49$) and superior (BA 7, $r=0.47$) parietal lobule, postcentral gyrus (BA 3, $r=0.46$), angular gyrus (BA 39, $r=0.41$), and precuneus (BA 7, $r=0.39$), in temporal regions such as the supramarginal gyrus (BA 40, $r=0.46$), superior temporal gyrus (BA 39, $r=0.43$), and middle temporal gyrus (BA 39, $r=0.38$), and in the precentral gyrus of the frontal lobe (BA 4, $r=0.41$).

The total scores of the avoidance and numbing items exhibited a significant positive correlation ($p<0.05$) with the P300 current source densities in parietal regions including the inferior (BA 40, $r=0.41$) and superior (BA 7, $r=0.39$) parietal lobule, the supramarginal gyrus (BA 40, $r=0.39$), and in temporal regions such as the superior (BA 39, $r=0.38$) and inferior (BA 20, $r=0.36$) temporal gyrus. In contrast, the P300 current source densities in frontal regions such as the superior (BA 9, $r=-0.40$) and middle frontal gyrus (BA 9, $r=-0.40$) exhibited a significant inverse correlation ($p<0.05$) with the total scores of avoidance and numbing items.

We also observed a significant positive correlation ($p<0.05$) between the total scores of hyper-arousal items (D1–D5) and the P300 current source densities in several frontal regions such as the precentral gyrus ($r=0.45$), the inferior ($r=0.42$), middle ($r=0.41$) and superior ($r=0.41$) frontal gyrus, and in temporal regions such as the superior ($r=0.39$), middle ($r=0.39$), and inferior ($r=0.38$) temporal gyrus, in the postcentral gyrus in the parietal lobe ($r=0.41$), and in the insula ($r=0.37$).

4. Discussion

The present study investigated the current source density of the altered P300 activity observed in PTSD patients in response to non-trauma-relevant stimuli in the auditory oddball task. We also examined the correlation between P300 current source density and clinical symptom severity. Both the P300 current source density and amplitude were significantly lower in PTSD patients than in healthy

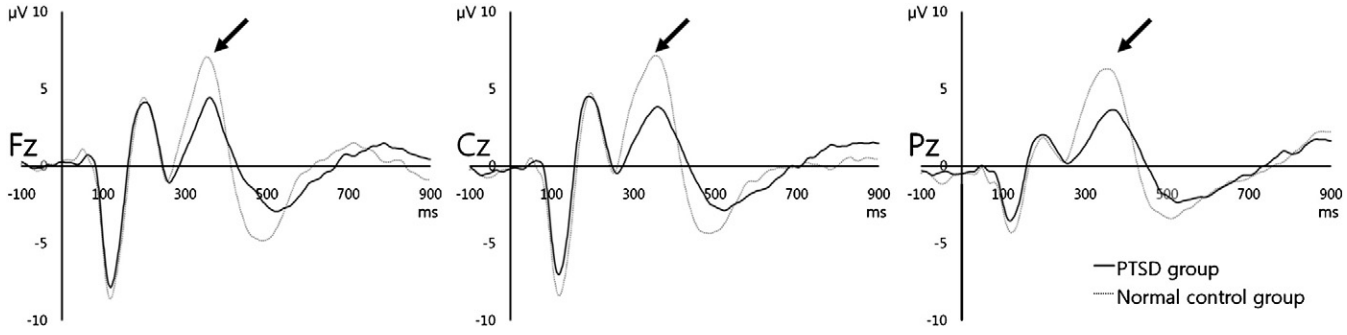

Fig. 1. Grand averages of the ERP waveforms at the Fz, Cz, and Pz electrodes for PTSD patients and normal controls. Arrows indicate the P300 peaks.

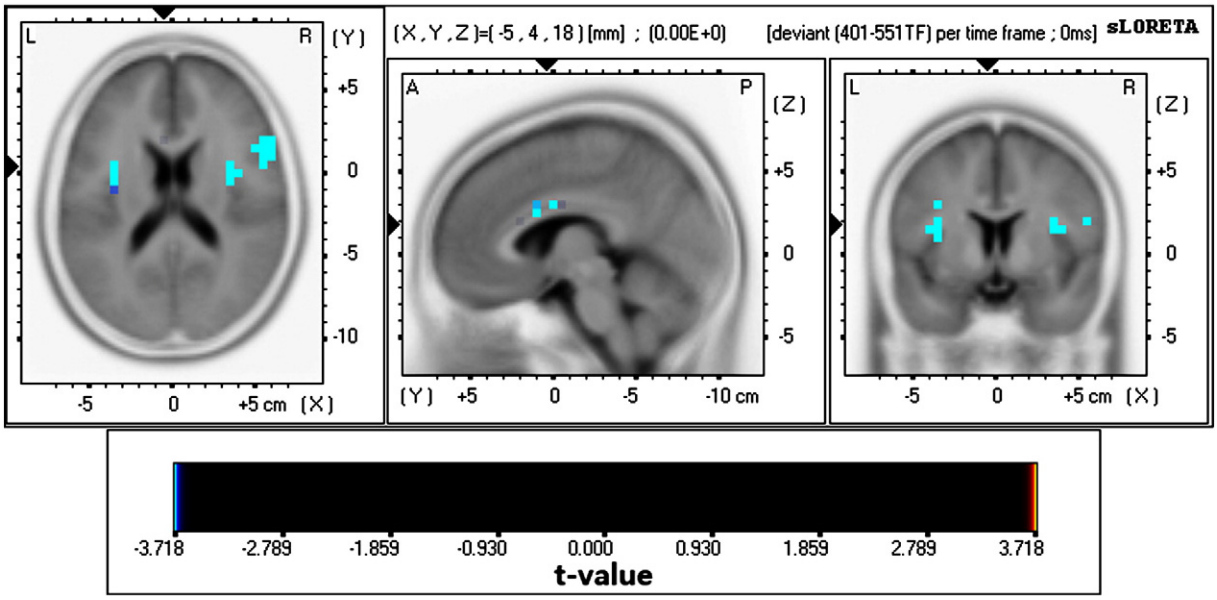

Fig. 2. sLORETA images of P300 current density showing significant differences between the PTSD and control groups. All voxels were thresholded at $p<0.05$.

controls. Furthermore, we found that PTSD symptoms were significantly correlated with the current source densities of various brain regions, and their correlation patterns varied depending on to the symptom characteristics.

Most previous imaging studies on PTSD have investigated responses to trauma-relevant stimuli. However, cognitive impairments (e.g., selective attention) in PTSD have also been found in response to non-trauma-relevant stimuli in neuropsychological and electrophysiological tests (Felmingham et al., 2002; McFarlane et al., 1993; Vasterling et al., 2002). The oddball paradigm using non-trauma-relevant stimuli has been applied widely in electrophysiological studies to assess the functioning of selective attention (Felmingham et al., 2002; Polich and Kok, 1995). When we consider that one of the important characteristics of anxiety disorders is intensified responses to trauma-relevant stimuli, the oddball paradigm can allow us to study the neural networks of information processing unaffected by emotional stimuli. In the present study, patients with PTSD exhibited a significant reduction in P300 amplitude compared to normal controls, but a normal P300 latency. This finding is consistent with previous P300 studies of PTSD. A study which employed meta-analysis techniques of ERPs in patients with PTSD suggested that ERP responses to neutral stimuli were reduced while enhanced ERP responses were elicited by trauma-related stimuli (Karl et al., 2006a). The P300 amplitude indicates neural activity that is related to the processing of new information (Donchin, 1981; Polich, 1996). Therefore the reduced P300 amplitude in patients with PTSD might suggest the reduced allocation of cognitive resources (Karl et al., 2006a).

The present study found that the P300 current source densities in the inferior frontal gyrus, precentral gyrus, insula, and anterior cingulate gyrus were significantly reduced in PTSD patients compared to normal controls. The inferior frontal cortex is known to be an important locus of inhibitory control, and its dysfunction during executive tasks was observed in the patients with PTSD (Aron et al., 2004; Falconer et al., 2008; Morey et al., 2008). Our result showing the reduced P300 current source densities in the inferior frontal cortex is consistent with previous finding that showed the reduction of blood oxygen-level-dependent (BOLD) activity during inhibition in the Go/No-Go task in patients with PTSD (Falconer et al., 2008). Decreased activity of the precentral gyrus may be relevant to disturbance of the inhibition of movement or the contrast-enhancing mechanism including anticipation or stimulus repetition, and may also reflect altered pain processing in PTSD (Geuze et al., 2007; Peyron et al., 1999). In addition, it is reported that the insular cortex is involved in the processing of sensory input and emotion and emotional induction with cognitive demand (Dalgleish, 2004; Kobayakawa et al., 1999; Phan et al., 2002; Pritchard et al., 2000). A recent study also found reduced gray matter volume and a lower level of activation in the insular cortex during word encoding and retrieval in patients with PTSD (Chen et al., 2009). Altered insular activity may be associated with a disturbance of the internally recalled emotions as well as the cognitive processing including memory (Phan et al., 2002). An fMRI study using the oddball paradigm suggested that anterior cingulate cortex networks are linked with attentional and affective functions (Fichtenholz et al., 2004). Functional and structural abnormalities of the anterior cingulate cortex in patients with PTSD have been reported consistently (Francati et al., 2007). A previous electrophysiological study found that the P300 peak was significantly lower in a PTSD group than in a non-PTSD group, and P300 amplitudes were positively correlated with the volume of the anterior cingulated cortex (Araki et al., 2005). The results of the present study are consistent with those of the previous neuropsychological and imaging studies of PTSD, which may account for a broad impairment of cognitive functions including executive, sensory and motor processing, emotion, memory, and attention in PTSD patients.

Furthermore, we also investigated the correlation between P300 current source density and clinical symptom severity assessed by various scales including DTS and SIP. Interestingly, the DTS scores were negatively correlated with the P300 current source density of the posterior cingulate gyrus. The posterior cingulate gyrus plays an important role in the higher cognitive functions such as episodic and autobiographical memory retrieval, coping with physical threats, and the processing of distressing material, which are also closely linked

Table 2
Brain regions showing significant differences in P300 current source density between the PTSD patients and normal controls. All brain regions were thresholded at $p<0.05$.

Brain lobe	Region	BA	MNI coordinates			Talairach coordinates			T score
			X	Y	Z	X	Y	Z	
Frontal lobe	Inferior frontal gyrus	9	−35	5	30	−35	6	27	−4.91
	Precentral gyrus	6	−35	0	30	−35	1	28	−4.82
Insula		13	−35	5	20	−35	6	18	−4.80
Limbic lobe	Anterior cingulate gyrus	33	−5	10	25	−5	11	22	−3.84

Note: BA, Brodmann's area; MNI, Montréal Neurological Institute.

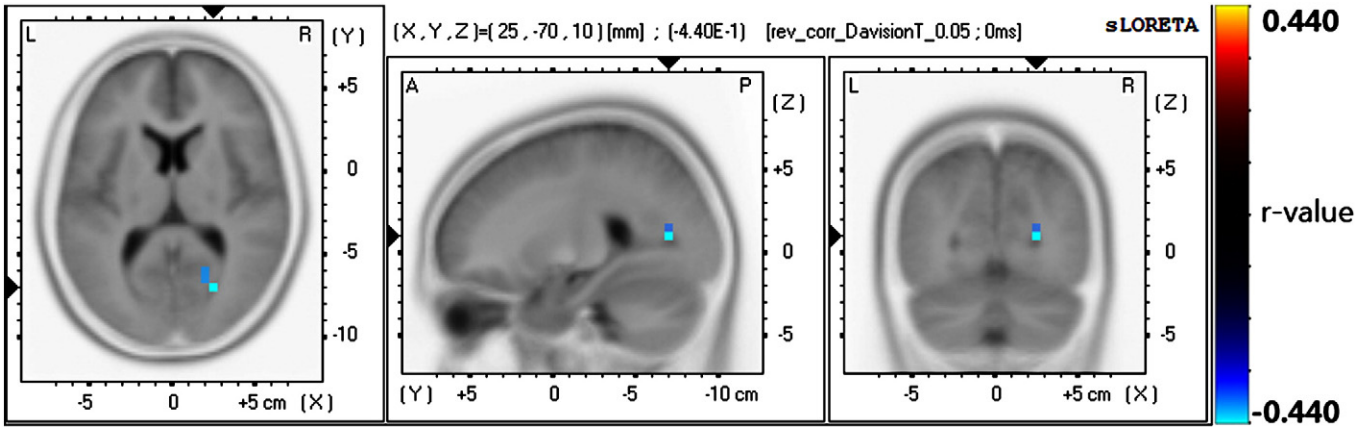

Fig. 3. Brain regions showing a significant correlation between P300 current density and K-DTS score in PTSD patients by Pearson correlation test. All voxels were thresholded at $p<0.05$. The region that showed a negative correlation was the posterior cingulate gyrus.

with symptoms of PTSD (Bremner, 2002; Buckner et al., 2008; Desgranges et al., 1998; Fischer et al., 1996; Maddock et al., 2001). A recent study found that patients with PTSD had a lower density of gray matter in the posterior cingulate gyrus that was correlated with trauma load, which suggested that the posterior cingulate gyrus is related to the processing of traumatic memories (Nardo et al., 2010).

In addition, the dysfunctional default mode network was suggested to have a major implication in patients with PTSD (De Luca et al., 2006; Gusnard et al., 2001; Lanius et al., 2006; Shulman et al., 2007). The default mode network is an organized network that is often deactivated during cognitive tasks and is related to tasks requiring self-reflection (Gusnard et al., 2001; Northoff and Bermpohl, 2004). The posterior cingulate gyrus was thought to be a crucial node in the default network, which links past memory with current environmental events and assesses events with regard to the relevance to the self (Moran et al., 2006; Nielsen et al., 2005). A substantial proportion of patients with PTSD reported dissociative symptoms that may be associated with altered self-perception (Lanius et al., 2002, 2005). Furthermore, a recent study found that the degree to which posterior cingulate gyrus is connected with other default mode network areas (precuneus, medial prefrontal cortex, and bilateral lateral parietal cortex) was lower in patients with PTSD than in healthy controls (Bluhm et al., 2009). Therefore, the results of the present study – revealing a negative correlation between posterior cingulate gyrus activity and PTSD symptom severity score – are in line with those of previous studies. In sum, it is like that posterior cingulate gyrus may be important in the processing of the trauma memory and self-perception, and may play an important role in the pathogenesis of PTSD.

We also found a significant positive correlation between the severity of two symptom categories (reexperiencing and increased arousal) of SIP and the P300 current source densities in multiple brain regions, especially in the frontal, temporal, and parietal lobes (Table 3A, C). It was previously suggested that the posterior part of the inferior frontal gyrus and temporoparietal junction are involved in stimulus-driven auditory attention (Doeller et al., 2003; Knight et al., 1989; Molholm et al., 2005; Rinne et al., 2005; Woods et al., 1993). Activation of the intraparietal sulcus, superior parietal lobule, middle frontal gyrus, frontal eye field, and premotor cortex during auditory attention has also been reported (Salmi et al., 2007). Furthermore, the elevated activation in posterior parietal attention and posterior somatosensory networks in PTSD may reflect generalized hyper-arousal and reduced sensory gating (Bryant et al., 2005). Previous studies suggested that coordinated activity among the frontal and parietal lobes, anterior cingulate gyrus, and cerebellum is involved in working memory and auditory attention (Braver et al., 1997; Clark et al., 2000; Doeller et al., 2003; Jonides et al., 1997; Knight et al., 1989; Molholm et al., 2005; Rinne et al., 2005; Salmi et al., 2007; Woods et al., 1993). Thus, the results of the present study suggest that reexperiencing and increased arousal to nonthreat stimuli in PTSD may be linked with the excessive activation of cognitive-attention networks and associated with dysfunction of the working memory and attention, Interestingly, however, we also found a significant negative correlation between the severity of avoidance and numbing symptoms and the P300 current source densities in frontal regions such as the superior and middle frontal gyrus, while these symptoms were positively correlated with those in the parietal and temporal lobes (Table 3B). It has been suggested that avoidance is secondary to reexperiencing, and that increased avoidance indirectly reflects increased reexperiencing, because the aim of avoidance behavior is to reduce reexperiencing symptoms (Hopper et al., 2007). However, it was reported that after successful treatment, a reduction in avoidance symptoms preceded a reduction in reexperiencing and increased arousal symptoms, and that avoidance and numbing symptoms may predict PTSD remission (Breslau et al., 2005; Feeny et al., 2000; Taylor et al., 2003). The present results suggest that the pathophysiological mechanisms underlying avoidance and numbing symptoms may differ from those underlying other PTSD symptoms such as reexperiencing and increased arousal.

The frontal lobe may play an important role in avoidance and numbing. Indeed, the findings of the fMRI study implicated several frontal regions in the voluntary suppression of negative affect, and that increased levels of negative affect reflect reduced recruitment of a top–down control mechanism (Phan et al., 2005). An animal study also found that lesions of the frontal cortex increased the freezing and fear response in animals (Morgan and LeDoux, 1995). It has been shown that increased activations in the subcortical structures such as the amygdala may be associated with the consolidation of the emotional memory of the traumatic event and increased arousal state in patients with PTSD, which may result in negative and distressful affect (Rauch et al., 2006). Successful control of the affect is related to the capacity to regulate negative emotional responses using effective cognitive strategy (Phan et al., 2005). The results of previous studies suggest that dysfunction of the frontal lobe leads to inadequate top–down regulation over subcortical hyperactivation and increased behavioral coping strategies such as avoidance. A recent review also suggested that the symptom of apathy, which is similar to restricted affect and diminished interest, reflects dysfunction in frontal-subcortical circuits (Bonelli and Cummings, 2007). Taken together, reduced frontal lobe regulation on subcortical activity can be postulated as a contributing factor to behavioral PTSD symptoms such as avoidance and numbing.

This study was subject to some limitations. Firstly, we could not control the medication in this study. Medication may affect working memory in patients with PTSD because SSRIs can alter the prefrontal dopamine and norepinephrine systems that are related to working memory (Bymaster et al., 2002; Clark et al., 2000). Therefore, we could

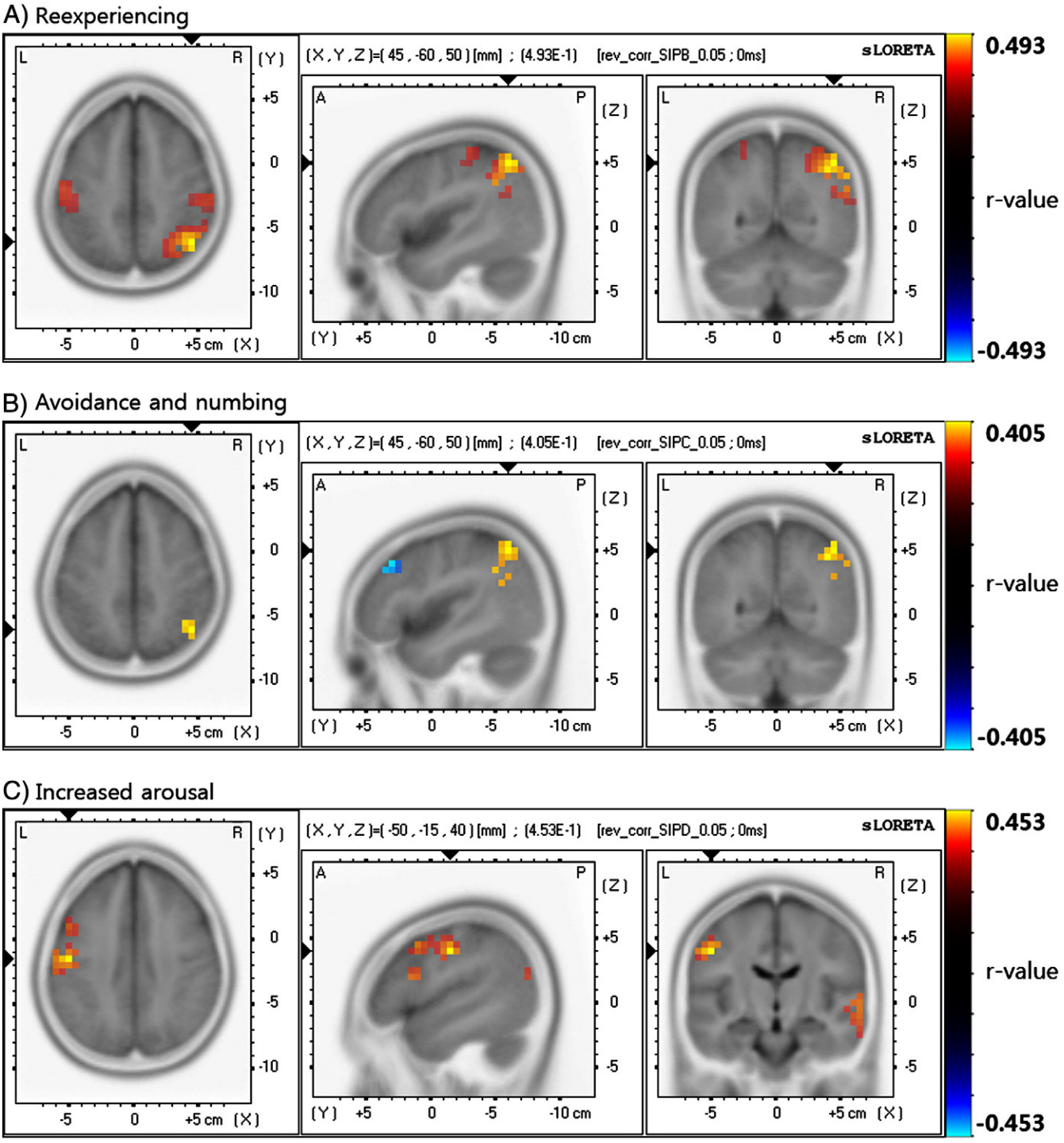

Fig. 4. Brain regions showing a significant correlation between P300 current densities and K-SIP scores such as for reexperiencing, avoidance, and numbing, and increased arousal in PTSD patients (Pearson's correlation test). All voxels were thresholded at $p<0.05$. The regions that showed a positive correlation with reexperiencing were the inferior and superior parietal lobule, posterior central gyrus, angular gyrus, precuneus, supramarginal gyrus, superior and middle temporal gyrus, and precentral gyrus (A). The regions that showed a positive correlation with avoidance and numbing were the inferior and superior parietal lobule, supramarginal gyrus, and superior and inferior temporal gyrus. The regions that showed a negative correlation with avoidance and numbing were the superior and middle frontal gyrus (B). The regions that showed a positive correlation with increased arousal were the precentral gyrus, the inferior, middle, and superior frontal gyrus, the superior, middle, and inferior temporal gyrus, the postcentral gyrus, and the insula (C).

not exclude the effect of medications on the P300 component. In this study, however, we investigated not only the differences in the P300 component between patients with PTSD and normal controls but also the correlation between the P300 current source density and clinical symptom severity. We think that consistent evidence exhibited by the correlation between specific neuroanatomical regions and clinical symptom severity cannot be fully accounted for by medication effects although they can confound the results of this study. Secondly, the depressive symptom was not fully eliminated. Patients with PTSD exhibited higher depressive symptoms compared to the normal controls. Therefore, depressive symptoms in addition to PTSD symptoms might have influenced the correlations between symptom severity and P300 current source density. However, we found no significant correlation between depressive symptoms (as assessed using BDI and HAMD-17) and P300 current source density. Thirdly, ERP components may be influenced by trauma exposure itself as well as PTSD, but in the

Table 3
Brain regions showing a significant correlation between the P300 current source densities and SIP scores in PTSD patients for reexperiencing (A), avoidance and numbing (B), and increased arousal (C) (Pearson's correlation test). All brain regions were thresholded at $p<0.05$.

Brain lobe	Region	BA	MNI coordinates			Talairach coordinates			r
			X	Y	Z	X	Y	Z	
A) Reexperiencing									
Parietal lobe	Inferior parietal lobule	40	45	−60	50	45	−56	49	0.49
	Superior parietal lobule	7	40	−60	50	40	−56	49	0.47
	Postcentral gyrus	3	60	−25	45	59	−22	43	0.46
	Angular gyrus	39	50	−65	30	50	−62	31	0.41
	Precuneus	7	25	−60	50	25	−56	49	0.39
Temporal lobe	Supramarginal gyrus	40	45	−50	35	45	−47	35	0.46
	Superior temporal gyrus	39	55	−60	25	54	−57	26	0.43
	Middle temporal gyrus	39	50	−65	25	50	−62	26	0.38
Frontal lobe	Precentral gyrus	4	−60	−20	45	−59	−17	42	0.41
B) Avoidance and numbing									
Frontal lobe	Superior frontal gyrus	9	40	35	40	40	36	35	−0.40
	Middle frontal gyrus	9	45	30	40	45	31	35	−0.40
Parietal lobe	Inferior parietal lobule	40	45	−60	50	45	−56	49	0.41
	Superior parietal lobule	7	40	−60	50	40	−56	49	0.39
	Supramarginal gyrus	40	45	−50	35	45	−47	35	0.39
Temporal lobe	Superior temporal gyrus	39	45	−55	25	45	−52	26	0.38
	Inferior temporal gyrus	20	−50	−5	−40	−50	−7	−33	0.36
C) Increased arousal									
Frontal lobe	Precentral gyrus	4	−50	−15	40	−50	−13	37	0.45
	Inferior frontal gyrus	45	−60	15	20	−59	15	18	0.42
	Middle frontal gyrus	8	−50	10	45	−50	12	41	0.41
	Superior frontal gyrus	8	40	15	55	40	17	50	0.41
Temporal lobe	Superior temporal gyrus	22	55	15	−5	54	14	−5	0.39
	Middle temporal gyrus	22	55	−10	−5	54	−10	−4	0.39
	Inferior temporal gyrus	21	65	−15	−20	64	−15	−16	0.38
Parietal lobe	Postcentral gyrus	3	−50	−20	40	−50	−18	38	0.41
Insula		13	45	5	5	45	5	4	0.37

Note: BA, Brodmann's area; MNI, Montréal Neurological Institute.

present study the measure of trauma exposure was not administered (Metzger et al., 2009). Lastly, ERP localization is not an actual measurement of the internal distribution of electrical activity, but a model of internal configuration of electrical activity. Therefore, a localization model may not fit the data exactly because of noise in the data (Luck, 2005). However, the real measurement of neuronal activity is invasive and cannot be applied to human subjects. Although neuroimaging techniques such as fMRI provide non-invasive means of localizing changes in blood flow by alterations of neuronal activity, changes in blood flow are so slow that fMRI cannot permit the measurement of most cognitive processes in real time (Luck, 2005).

LORETA images have been reported to provide good estimates of the localization for activated brain regions identified with fMRI (Mulert et al., 2004; Sumiyoshi et al., 2009) and are capable of indicating widely distributed or multiple oriented electrical activity in real time, which are difficult to model with other dipole methods including BESA (Gallinat et al., 2002).

In correlation analyses, we included additional brain regions which did not show significant differences between patients and controls in P300 current source density. The implications of the results of these correlation analyses are exploratory and need to be verified.

Despite its limitations, this study had an advantage in employing a dimensional approach in investigating the correlation between state symptom severity and P300 current source density.

In conclusion, the findings of the present study in the P300 component suggest that patients with PTSD suffer from impairments of several domains of cognitive functions, such as executive function and attention, as well as emotional disturbances, such as anxiety. Additionally, these cognitive impairments are not limited to trauma-relevant stimuli, but are also seen with neutral stimuli. The results of this study further indicate that avoidance and numbing are associated with decreased frontal lobe activity, and that their neural mechanisms might differ from those of other PTSD symptoms, reexperiencing and increased arousal. These results support Foa et al's notion that different PTSD symptoms may represent distinct pathological processes and that classifying PTSD patients with different symptom patterns into the same category may be problematic in understanding PTSD psychopathology. In addition, these findings suggest that avoidance and numbing may not be just secondary to other PTSD symptoms, yet play an important role in the genesis of PTSD symptoms.

Thus, the present findings demonstrate that the P300 current source density might reflect the pathophysiology of PTSD, and that various neural networks might contribute to the symptom characteristics of PTSD. The integration of the results of this study with other biochemical, neuroimaging, and behavioral assessment techniques will provide a more comprehensive understanding of the effects of PTSD on the brain and on cognitive-perceptual functioning.

Acknowledgment

This work was supported by Grant from Inje University, 2006.

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