Machine-learning-based classification between post-traumatic stress disorder and major depressive disorder using P300 features

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ABSTRACT

Background: The development of optimal classification criteria for specific mental disorders which share similar symptoms is an important issue for precise diagnosis. We investigated whether P300 features in both sensor-level and source-level could be effectively used to classify post-traumatic stress disorder (PTSD) and major depressive disorder (MDD).
Method: EEG signals were recorded from fifty-one PTSD patients, 67 MDD patients, and 39 healthy controls (HCs) while performing an auditory oddball task. Amplitude and latency of P300 were evaluated, and the current source analysis of P300 components was conducted using sLORETA. Finally, we classified two groups using machine-learning methods with both sensor- and source-level features. Moreover, we checked the co-morbidity effects using the same approaches (PTSD-mono diagnosis (PTSDm, $n = 28$) and PTSD-comorbid diagnosis (PTSDc, $n = 23$)).
Results: PTSD showed significantly reduced P300 amplitudes and prolonged latency compared to HCs and MDD. Moreover, PTSD showed significantly reduced source activities, and the source activities were significantly correlated with symptoms of depression and anxiety. Also, the best classification accuracy at each pair was as follows: 80.00% (PTSD-HCs), 67.92% (MDD-HCs), 70.34% (PTSD-MDD), 82.09% (PTSDm-HCs), 71.58% (PTSDm-MDD), 82.56% (PTSDc-HCs), and 76.67% (PTSDc- MDD).
Conclusion: Since abnormal P300 reflects pathophysiological characteristics of PTSD, PTSD patients were well-discriminated from MDD and HCs when using P300 features. Thus, altered P300 characteristics in both sensor- and source-level may be useful biomarkers to diagnosis PTSD.

1. Introduction

Shared symptoms of post-traumatic stress disorder (PTSD) and major depressive disorder (MDD), such as emotional numbing, dysphoria, poor sleep, irritability, and difficulties with concentration, can have a number of adverse effects on individuals (Elhai et al., 2011; Gros et al., 2012; Post et al., 2011). Thus, more efforts have been made to understand the unique biomarkers of these diseases to enhance diagnostic accuracy by minimizing burdens of patients and care providers, as various neurophysiology-based biomarkers could function as useful assistance tools for the diagnosis of both diseases (Kemp et al., 2007; Kennis et al., 2013; Whalley et al., 2009).

In particular, dynamic neural activities could well reflect the intrinsic characteristics of each disorder. According to functional magnetic resonance imaging (fMRI) research (Whalley et al., 2009), patients with PTSD and MDD showed different neural responses when reading emotional texts, with PTSD patients exhibiting enhanced hemodynamic activity in the hippocampus, precuneus and cingulate cortex compared to MDD patients and healthy controls (HCs). With a number of shared symptoms, MDD and PTSD are often comorbid, and these patients with both pathologies exhibit different brain activation patterns compared to individuals with MDD or PTSD, alone. More specifically, individuals with both MDD and PTSD exhibit reduced amygdala and frontal activation compared to PTSD patients without MDD (Kemp et al., 2007). Also, the synchrony between the anterior cingulate cortex (ACC) and other brain areas in PTSD patients with MDD was enhanced compared to PTSD patients without depression, and the disrupted ACC connectivity was closely related to symptoms of

avoidance and emotional numbing of PTSD patients with MDD (Kennis et al., 2013). A number of previous research has focused on neuronal activities during the processing of emotional information in two disorders. However, the altered cognitive process also is an important pathology of PTSD and MDD (Ehlers and Clark, 2000; Hammar and Årdal, 2009; Lee et al., 2012).

The event-related potentials (ERPs) are a useful measure for examining cognitive processes that occur for very short periods of time (Pfurtscheller and Da Silva, 1999). Particularly, P300 is well known to be closely associated with cognitive processes (Linden, 2005; Polich, 2007), and a large body of research has documented abnormal P300 as one of many characteristics of both MDD and PTSD. According to previous research, PTSD showed reduced P300 amplitude and prolonged latency compared to HCs, and altered P300 amplitude was significantly related to cognitive impairment, attentional allocation problems (Javanbakht et al., 2011a; Lobo et al., 2015), and other PTSD symptoms such as numbing (Araki et al., 2005; Bae et al., 2011; Felmingham et al., 2002; Kim et al., 2009). Individuals with MDD showed decreased P300 amplitudes compared to HCs as well as PTSD (Mumtaz et al., 2015b). Meanwhile, P300 latencies were prolonged in MDD compared to HCs (Kawasaki et al., 2004; Vandoolaeghe et al., 1998), Moreover, the abnormal source activities of MDD in the frontal and the temporo-parietal area were revealed by a source imaging study (Kawasaki et al., 2004).

The unique P300 characteristics could be useful biomarkers when classifying psychiatric disorders from HCs using machine-learning method. In case of the differentiating between MDD patients from HC using P300, the classification accuracy of 90.5% was achieved by the logistic regression classifier (Mumtaz et al., 2015a). Moreover, the MDD patients were differentiated with relatively high classification accuracy using various neurological measures such as power spectral density as well as ERPs (Mumtaz et al., 2015b; Mumtaz et al., 2017). However, previous machine-learning studies which attempted to predict PTSD used only symptoms scores as the criteria features, lacking a functional neurological measure such as P300 (Karstoft et al., 2015; Leightley et al., 2019). Moreover, the study which directly differentiated PTSD and MDD using P300 features at both sensor- and source-level has not yet been reported.

The aim of this study is to investigate differences of P300 features in both sensor- (amplitude and latency) and source-level (source activities) between PTSD and MDD using an auditory oddball task. Additionally, we investigated the possible relationships between P300 features and symptom severity scores. Finally, we examined the possibility of P300 characteristics as a biomarker by differentiating PTSD, MDD, and HCs using a machine learning methodology with sensor- and source-level P300 features. To the best of our knowledge, this is the first ERP study to investigate the differences of the cognitive process between PTSD and MDD and further to differentiate two disorders based on machine learning measure.

2. Material and methods

2.1. Participants

Fifty-one PTSD patients, 67 MDD patients, and 39 HCs were recruited for this study from the Psychiatry Department of Inje University Ilsan Paik Hospital. The patients' diagnoses were based on the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) Axis I Psychiatric Disorders by a board-certified psychiatrist. Patients were excluded if they accorded with the following contents: 1) abnormality of the central nervous system, 2) medical histories of alcohol or drug abuse, 3) mental retardation, 4) a history of head injuries with loss of consciousness and experience with electrical therapy, 5) psychotic symptoms lasting for at least 24 h. To control for the influence of anxiety, the MDD patients with comorbid anxiety disorders (e.g. general anxiety disorder, panic disorder, and obsessive-compulsive disorder) were excluded by an expert clinician with the DSM-IV diagnostic criteria. HCs were recruited from the local community through local newspapers and posters. A person without any psychiatric medical history was recruited for HCs. If HCs took or have taken any kinds of psychotropic medication, they were excluded in the study. All participants provided written informed consent, and the study protocol was approved by the Institutional Review Board of Inje University Ilsan Paik Hospital (2015-07-025 and 2015-07-048-002).

Beck Anxiety Inventory (BAI) (Beck and Steer, 1990) were used to evaluate anxiety symptom (mild: 8–15; moderate: 16–25; and severe: 26–63) (Yook and Kim, 1997). To investigate depressive symptom, and Beck Depression Inventory (BDI) (Beck et al., 1996) were used (mild: 14–19; moderate: 20–28; and severe: 29–63) (Cha et al., 2018). Also, Impact of Event Scale-Revises (IES-R) (Weiss, 2007) was used to check the responses to a traumatic event of PTSD patients (mild: 0–24; moderate: 25–39; and severe: 40–59; very severe: ≥ 60) (Lee et al., 2016). The prevalence of caseness in the PTSD patients was as follows: sever motor vehicle accidents = 44 (86.24%), physical or sexual violence = 2 (3.92%), other accidents (e.g. building collapse) = 5 (9.81%). Demographic data and the mean and standard deviation (SD) of psychiatric severity scores in each group are reported in Table 1.

2.2. EEG recordings and ERP analysis

The stimuli used for the auditory oddball paradigm were composed of target tones with 1500 Hz tone frequency and standard tones with the 1000 Hz tone frequency. The duration of each stimulus was set to 100 ms, and rising and falling times were set to 10 ms. Four-hundred pure tone stimuli consisting of 15% target tones and 85% standard tones were presented in a random order with an inter-stimulus interval of 1500 ms. The participants were required to press a response button when the target tones were presented.

EEG was recorded using a NeuroScan SynAmps2 (Compumedics

Table 1

Demographic data of post-traumatic stress disorder, major depressive disorder and healthy controls. The *p* value represents significant differences among three groups (total PTSD, MDD and HCs) by one-way ANOVA, and comparison pairs were represented by the bold letter.

	PTSD			MDD	HCs	*p*
	PTSDm	PTSDc	Total PTSD			
Cases (N)	28	23	**51**	**67**	**39**	
Gender (male/female)	14/14	10/13	**24/27**	24/43	18/21	0.429
Age (years)	43.50 ± 8.88	42.09 ± 12.33	**42.86 ± 10.49**	42.09 ± 9.83	**38.74 ± 9.05**	0.118
Education (years)	13.64 ± 3.11	12.83 ± 3.16	**13.27 ± 3.13**	13.54 ± 3.53	14.47 ± 2.15	0.198
Symptom score						
BDI	26.64 ± 12.66	26.50 ± 12.88	26.58 ± 12.62	25.81 ± 8.39		
BAI	28.71 ± 15.75	31.38 ± 15.90	29.86 ± 15.71	24.43 ± 9.83		
IES-R	53.38 ± 20.59	55.00 ± 20.72	53.21 ± 20.80			

PTSD: post-traumatic stress disorder; PTSDm: PTSD-mono diagnosis; PTSDc: PTSD-comorbid diagnosis; MDD: major depressive disorder; HCs: healthy controls; BDI: Beck Depression Inventory, BAI: Beck Anxiety Inventory, IES-R: Impact of Event Scale-Revises.

USA, El Paso, TX, USA) from 64 Ag/AgCl scalp electrodes evenly mounted on a QuikCap according to the extended 10–20 international system (references: M1 and M2). EEG was recorded with a 1- to 100 Hz band-pass filter at a sampling rate of 1000 Hz. The eye artifacts were removed using established mathematical procedures(Semlitsch et al., 1986), and other gross artifacts were rejected by visual inspection. Artifacts-free EEG was band-pass filtered at 1- to 30 Hz and epoched from 100 ms before the target onset to 900 ms after the target onset. The epochs were rejected if they contained significant physiological artifacts (± 75 μV) at any electrodes. Artifact-free epochs were averaged across trials for ERP analysis. P300 was defined as a maximum peak between 250 and 500 ms after the target onset at five electrodes (Fz, Cz, Pz, T7, and T8) (Bharath et al., 2000; Hopfinger and Maxwell, 2005; Lazzaro et al., 1997).

2.3. Source analysis

Standardized low-resolution brain electromagnetic tomography (sLORETA) is widely used for solving the EEG inverse problem when estimating neural activation of the brain. sLORETA assumes that the current source density (CSD) of one voxel is synchronized to that of the surrounding voxels to calculate a particular solution. CSD was estimated using the realistic head model constructed from the MNI152 standard template. The source space was restricted to the cortical gray matter, yielding 6239 voxels with $5 \times 5 \times 5$ mm resolution. The time windows for estimating P300 CSD were set as the mean P300 latency ± two standard deviations in each group (Kim et al., 2014): PTSD: 289–453 ms; MDD: 284–429 ms; HCs: 302–416 ms. All source estimation procedures were done using the open sLORETA software (http://www.uzh.ch/keyinst/loretaOldy.htm).

2.4. Statistical analysis

A one-way ANOVA was performed to evaluate differences of P300 amplitude and latency among the three groups at each electrode. When a significant difference was revealed, a post hoc analysis was performed using an independent *t*-test with Bonferroni corrected *p*-value.

Also, we checked the effects of comorbidity in two groups of patients on P300 amplitudes and latencies. We divided patients into three groups as follows: 1) PTSD-mono diagnosis (PTSDm, *n* = 28), they showed only PTSD symptoms without comorbidity; 2) PTSD-comorbid diagnosis (PTSDc, *n* = 23) groups, they showed mood swings and emotional problems that are symptoms of disorders such as depression and anxiety; 3) MDD (*n* = 67). To eliminate effects of anxiety, the patients with an anxiety disorder were strictly excluded from our study. To find possible differences between three groups, we performed the one-way ANOVA and post hoc analysis.

When a significant difference was found in sensor-level, statistical analysis of CSD between groups was performed using the statistical non-parametric mapping method (SnPM) that was implemented in the sLORETA software. The estimated voxel activation was averaged over the calculated time frame and tested for voxel-by-voxel with independent t-test for the 6239 voxels, followed by adjustments for multiple comparisons. Furthermore, the relationships between P300 features (P300 peak amplitude, latency, and CSD) and psychiatric scores of patients were investigated using Spearman's correlation method with 5000 bootstrap resamples.

2.5. Classification model and feature selection

Additionally, we differentiated patient groups and HCs using the computed sensor and source activities to check their potential usability as a biomarker. To discriminate groups, we set seven different classification pairs: 1) PTSD-HCs; 2) MDD-HCs; 3) PTSD-MDD; 4) PTSDm-HCs; 5) PTSDm-MDD; 6) PTSDc-HCs; 7) PTSDc-MDD.

Both sensor-level and source-level P300 features were used to find

optimal features to discriminate groups by each classification pair. The used features were as follows: sensor-level – each of the sixty-two P300 amplitudes and latencies (total 124); source-level – CSD in different brain regions showing significantly different between groups. In order to decrease the computational cost and avoid the overfitting by the use of large numbers of features, feature selection based on Fisher score (Alimardani et al., 2018; Gu et al., 2012) was used. The higher Fisher score for each feature represents the better discrimination capability between the two groups. The features with relatively higher Fisher scores were selected for the classification, with the number of features ranging from 1 to 20 (Shim et al., 2016). The classification accuracy was evaluated using a two-class linear support vector machine (SVM) classifier (Alimardani et al., 2018; Orru et al., 2012) with a leave-one-out cross-validation (LOOCV) method for each feature set (Shim et al., 2016). To compute LOOCV, the only one subject was used for validating the model and remaining subjects (N-1) were used for training of the model (Al-Kaysi et al., 2017; Wang et al., 2015).

3. Results

3.1. P300 amplitude and latency

Regarding P300 amplitude, there were significant differences among three groups at all electrodes (Fz: $F(2, 154) = 8.08$, $p = .000$; Cz: $F(2, 154) = 8.89$, $p = .000$; Pz: $F(2, 154) = 8.49$, $p = .000$; T7: $F(2, 154) = 3.45$, $p = .034$; T8: $F(2, 154) = 9.53$, $p = .000$). The significant difference at each electrode after the post hoc analysis with adjusted *p* value using Bonferroni methods were as follows: 1) PTSD showed significantly reduced P300 amplitude compared to HCs at Fz (adjusted *p* (adj*P*) = 0.002), Cz (adj*P* = 0.000), Pz (adj*P* = 0.001), T7 (adj*P* = 0.032), and T8 (adj*P* = 0.000); 2) PTSD showed significantly reduced P300 amplitude compared to MDD at Fz (adj*P* = 0.002), Cz (adj*P* = 0.004), Pz (adj*P* = 0.004), and T8 (adj*P* = 0.016).

Also, there were significant differences among three groups of latency at Cz ($F(2, 154) = 3.20$, $p = .043$; Pz ($F(2, 154) = 4.90$, $p = .009$) and T8 ($F(2, 154) = 4.59$, $p = .012$). The results were as follows: 1) PTSD showed significantly delayed latency compared to HCs at Pz (adj*P* = 0.038); 2) PTSD showed significantly delayed latency compared to MDD at Cz (adj*P* = 0.038), Pz (adj*P* = 0.015), and T8 (adj*P* = 0.010). The sensor-level results of amplitude and latency in each group are reported in the Supplementary Table 1, and Fig. 1a and b. represent P300 amplitude in each group at five electrodes. Topographical distributions of P300 in each group are represented in Fig. 1c.

3.2. Source localization using sLORETA

In the source-level, we performed a comparison of CSD between two groups (e.g., PTSD vs. HCs) because the statistical method provided by sLORETA software could apply only to a comparison of two groups. First, PTSD compared to HCs showed significantly decreased CSD in anterior cingulate (AC), cingulate gyrus (CG), cuneus, fusiform gyrus, inferior occipital gyrus (IOG), inferior temporal gyrus(ITG), insula, lingual gyrus, medial frontal gyrus (MFG), middle occipital gyrus (MOG), parahippocampal gyrus, posterior cingulate (PC), precuneus, sub-gyral, superior temporal gyrus (STG), uncus (*p* < .05; Table 2, Fig. 2a. Secondly, PTSD compared to MDD showed significantly reduced CSD in AC, CG, cuneus, insula, MFG, MTF, parahippocampal gyrus, PC, precuneus, sub-gyral, superior occipital gyrus (SOG) and STG (*p* < .05; Table 2, Fig. 2b).

3.3. Correlation between P300 characteristics and psychiatric scales

Sensor-level features were not correlated with psychiatric scale.

In case of source-level features, there were significant relationships between CSD and symptom scores (BDI and BAI) in PTSD: 1) BDI: fusiform gyrus($r = -0.328$, $p = .002$); IOG ($r = -0.434$, $p = .002$);

a. P300 waveforms in pure patients

b. P300 waveforms in patients with comorbidity

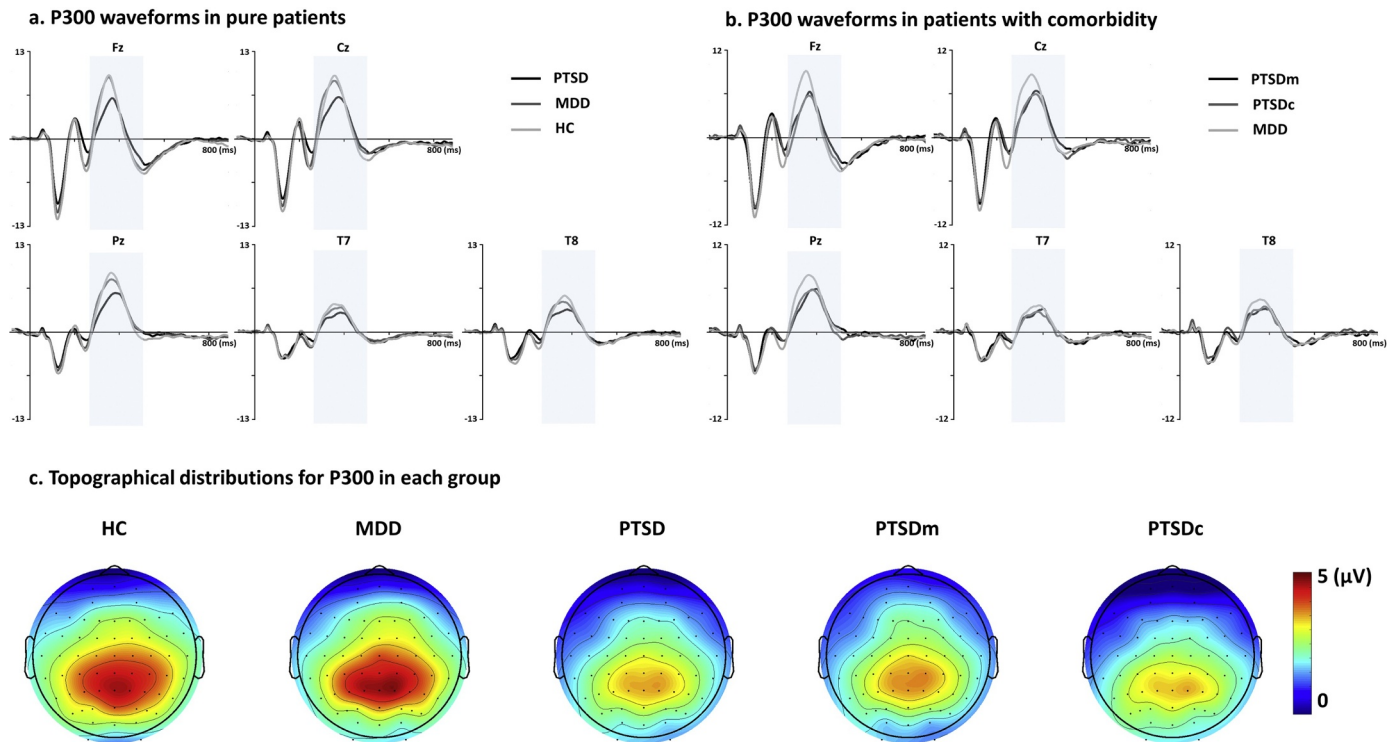### c. Topographical distributions for P300 in each group

Fig. 1. P300 event-related potential (ERP) waveforms at Fz, Cz, Pz, T7, and T8 electrodes. a) ERP waveforms in post-traumatic stress disorder (PTSD), major depressive disorder (MDD), and healthy controls (HCs). b) P300 ERP waveforms in patients with comorbidity (post-traumatic stress disorder-comorbid diagnosis (PTSDc), post-traumatic stress disorder-mono diagnosis (PTSDm) and MDD). c) Topographical distributions of the grand averaged P300 ERP component over 250–500 ms in each group.

lingual gyrus ($r = -0.423$, $p = .002$); MOG ($r = -0.316$, $p = .025$); PC ($r = -0.293$, $p = .039$); 2) BAI: fusiform gyrus($r = -0.375$, $p = .008$); IOG ($r = -0.342$, $p = .016$); lingual gyrus ($r = -0.385$, $p = .006$); MOG ($r = -0.326$, $p = .022$); PC ($r = -0.322$, $p = .024$).

3.4. Comorbidity check

Significant differences among three groups were found at Fz, Cz and Pz electrode (Fz: F(2, 115) = 5.56, $p = .005$; Cz: F(2, 115) = 5.35, $p = .006$; Pz: F(2, 115) = 5.16, $p = .007$). The significant differences at each electrode after the post hoc analysis with adjusted p-value using Bonferroni methods have appeared only between PTSDc and MDD (Fz (adj$P = 0.012$), Cz (adj$P = 0.013$), and Pz (adj$P = 0.017$)). To provide more specific information about comorbidity factors, we represent P300 waveforms and topographical distributions of three groups in Fig. 1b and Supplementary Table 1. Also, there were significant differences among three groups of latency at Pz (F(2, 115) = 4.46, $p = .014$) and T8 (F(2, 115) = 4.11, $p = .019$). Likewise amplitude analysis, the post hoc analysis with adjusted p-value using Bonferroni correction methods was performed, PTSDm showed a significantly prolonged latency compared to MDD at Pz (adj$P = 0.012$). Moreover, PTSDc showed decreased source activations in AC, CG, MFG and STF compared to MDD ($p < .05$; Table 2, Fig. 2c). However, there was no significant difference in CSD between PTSDm and MDD.

3.5. Classification results

Source-level features were extracted from different 23 brain regions showing significant statistical differences between all possible pairs of groups, and the list of ROIs was reported in the supplementary information. Best classification accuracies at each classification pair were as follows: 1) PTSD-HCs: 80.00%; 2) MDD-HCs: 67.92%; 3) PTSD-MDD: 70.34%; 4) PTSDm-HCs: 82.09%; 5) PTSDm-MDD: 71.58%; 6) PTSDc-

HCs: 82.56%; 7) PTSDc-MDD: 76.67%. The best classification accuracy, specificity, and sensitivity in each classification pairs are summarized in Table 3. More details on the features used for each classification pairs are described in the supplementary information.

4. Discussion

In this study, we investigated neurocognitive abnormalities of PTSD and MDD in sensor- and source level using P300 and differentiated PTSD, MDD, and HCs based on a machine-learning method. The major findings were as follows: (1) PTSD showed significantly reduced P300 amplitude and latency compared to HCs and MDD; (2) PTSD showed significantly reduced CSD in several regions compared to HCs as well as MDD; (3) CSD of PTSD in fusiform gyrus, IOG, lingual gyrus, MOG, and PC was negatively correlated with both BDI and BAI scores; (4) in machine-learning-based classification, the best classification accuracies for each pair were 80.00% (PTSD-HCs), 67.92% (MDD-HCs), 70.34% (PTSD-MDD), 82.09% (PTSDm-HCs), 71.58% (PTSDm-MDD), 82.56% (PTSDc-HCs), and 76.67% (PTSDc- MDD).

4.1. Abnormal P300 amplitude and latency

Most prior PTSD research has reported reduced P300 amplitude, and in some cases, reported prolonged P300 latency compared to HCs (Javanbakht et al., 2011b). Moreover, significant correlations between P300 features and various symptom scores (STAI, IES-R, and CAPS) are also well documented (Javanbakht et al., 2011b; Lobo et al., 2015). Despite these well-replicated findings, some studies have failed to find significant relationships between PTSD symptoms and P300 (Kimble et al., 2010; Lamprecht et al., 2004), and some have even found the relationships in an opposite nature(Attias et al., 1996). In the case of MDD, the results of previous ERP studies have largely been inconsistent (Mumtaz et al., 2015b). Some researchers have reported reduced P300

Table 2
Brain regions showing significant P300 source activity differences between patients and healthy controls.

ROI (structure)	MNI coordination			Talairach coordinates			T score
	X	Y	Z	X	Y	Z	
PTSD < HCs							
Anterior Cingulate	10	25	30	10	26	26	−4.11
Cingulate Gyrus	0	−40	25	0	−38	25	−4.07
Cuneus	−5	−65	5	−5	−63	8	−4.10
Fusiform Gyrus	−25	−50	−15	−25	−49	−10	−4.07
Inferior Occipital Gyrus	−25	−90	−20	−25	−88	−12	−4.10
Inferior Temporal Gyrus	40	−20	−35	40	−21	−28	−4.08
Insula	30	−30	15	30	−28	15	−4.11
Lingual Gyrus	−10	−55	0	−10	−53	3	−4.13
Medial Frontal Gyrus	−15	25	35	−15	26	31	−4.07
Middle Occipital Gyrus	−20	−90	−15	−20	−88	−8	−4.40
Parahippocampal Gyrus	−10	−50	0	−10	−48	2	−4.18
Posterior Cingulate	−5	−60	5	−5	−58	8	−4.25
Precuneus	0	−70	15	0	−67	17	−4.07
Sub-Gyral	−15	−45	−10	−15	−44	−6	−4.09
Superior Temporal Gyrus	35	−35	15	35	−33	15	−4.13
Uncus	30	−15	−35	30	−16	−29	−4.11
MDD < HCs							
Cuneus	−5	−65	5	−5	−63	8	−4.43
Fusiform Gyrus	−20	−60	−15	−20	−59	−10	−4.06
Lingual Gyrus	−5	−65	0	−5	−63	3	−4.08
Parahippocampal Gyrus	−10	−50	0	−10	−48	2	−4.05
Posterior Cingulate	−5	−60	5	−5	−58	8	−4.07
PTSD < MDD							
Angular gyrus	−35	−80	30	−35	−76	31	−4.32
Anterior Cingulate	10	25	30	10	26	26	−3.96
Cingulate Gyrus	−20	−45	25	−20	−42	25	−3.89
Cuneus	−25	−85	25	−25	−81	27	−3.91
Insula	−40	−45	20	−40	−43	21	−3.90
Medial Frontal Gyrus	15	25	35	15	26	31	−3.90
Middle Frontal Gyrus	20	20	45	20	21	40	−4.11
Middle Temporal Gyrus	−35	−60	20	−35	−57	21	−3.96
Parahippocampal Gyrus	15	−5	−15	15	−5	−12	−3.93
Posterior Cingulate	−5	−40	25	−5	−38	25	−3.90
Precuneus	−20	−45	30	−20	−42	30	−3.91
Sub-Gyral	−30	−60	25	−30	−57	26	−4.25
Superior Frontal Gyrus	20	15	50	20	17	45	−3.95
Superior Occipital Gyrus	−30	−85	25	−30	−81	27	−3.94
Superior Temporal Gyrus	−35	−55	20	−35	−52	21	−3.91
Transverse Temporal Gyrus	−35	−35	10	−35	−33	11	−4.09
PTSDc < MDD							
Anterior Cingulate	−10	25	30	−10	26	26	−4.42
Cingulate Gyrus	−15	10	40	−15	12	36	−4.28
Inferior frontal gyrus	35	5	30	35	6	27	−4.36
Medial Frontal Gyrus	−15	25	35	−15	26	31	−4.29
Superior Temporal Gyrus	−35	−55	25	−35	−52	26	−4.28

PTSD: post-traumatic stress disorder; HCs: healthy controls; MDD: major depressive disorder; PTSDc: PTSD-comorbid diagnosis; MNI: Montreal Neurological Institute.

amplitudes (Kawasaki et al., 2004; Vandoolaeghe et al., 1998), while others have found no significant difference between MDD and HCs (Bruder et al., 2012). Moreover, there have been failed attempts to replicate findings that prolonged P300 latency could be a biomarker for MDD (Vandoolaeghe et al., 1998), whereas it was not replicated to others (Kaustio et al., 2002).

The amplitude of P300 is related to cognitive functioning such as context updating, attention, and memory, and latency is affected by the speed of information processing (Linden, 2005; Polich, 2007). In our study, PTSD showed reduced P300 amplitudes and prolonged latencies compared to HCs and MDD, which is consistent with previous studies. Patients with PTSD have difficulty allocating the attentional resources for cognitive processing, and the processing speed is slow compared to both MDD and HCs. That is, the overall cognitive system of PTSD might be impaired compared to MDD as well as HC.

4.2. Altered source activation of P300 and the relationships with symptom scores

In the present study, PTSD showed significantly reduced CSD of the cingulate (AC, CG, and PC), frontal (MFG and IFG), occipital (IOF, MOG, cuneus, precuneus, and lingual gyrus), temporal (fusiform gyrus, and sub-gyral), insular and parahippocampal gyrus compared to HCs. Also, those PTSD individuals showed smaller CSD in cingulate (AC, CG, and PC), middle frontal gyrus, occipital (SOG, cuneus, and precuneus), temporal (MTF, STG, fusiform gyrus, and sub-gyral), insula and parahippocampal gyrus compared to MDD. Moreover, reduced source activation has shown negative correlations with BDI and BAI (in the fusiform gyrus, IOG, lingual gyrus, MOG, and PC) in PTSD.

It is well-known that individuals with PTSD suffered from abnormal cognitive functioning, including not only trauma memories and negative appraisals, but also atypical automatic information processing (Ehlers and Clark, 2000), which has been documented in neuroimaging
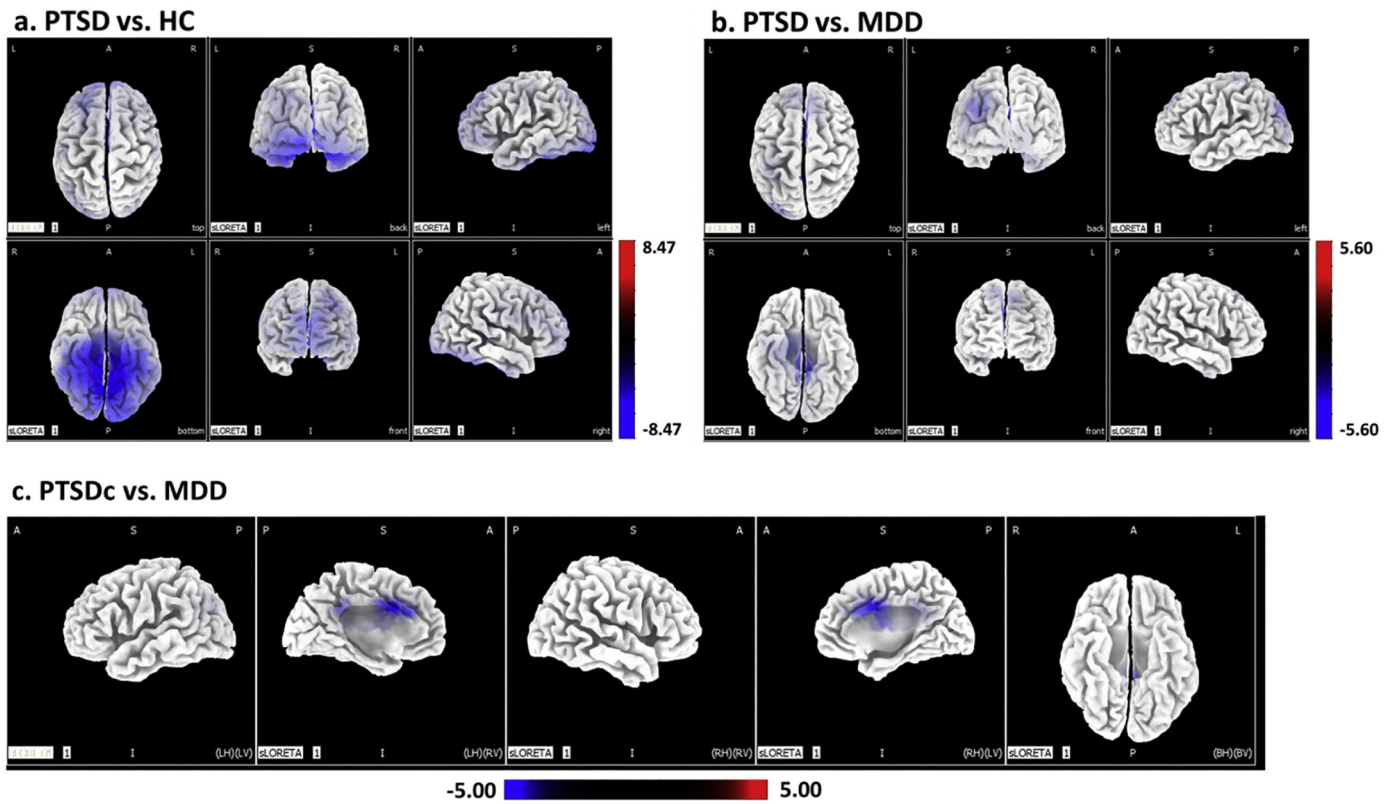
Fig. 2. Brain regions showing significant P300 source activity difference between the two groups. a) The blue color means the significantly reduced source activation of post-traumatic stress disorder (PTSD) compared to healthy controls (HCs). b) PTSD showed the significantly reduced source activation compared to major depressive disorder (MDD), and reduced activities are represented by blue color. c) The blue color means the significantly reduced source activation of post-trauma stress disorder-comorbid diagnosis (PTSDc) compared to and major depressive disorder (MDD).

Table 3
Maximum classification accuracies, specificities and sensitivities (unit: %) for three different feature sets (sensor, source, and sensor + source) for seven different classification pairs. The bold letter meant the best classification accuracy at each classification pair.

Classification pair	Sensor			Source			Sensor + source		
	Accuracy	Specificity	Sensitivity	Accuracy	Specificity	Sensitivity	Accuracy	Specificity	Sensitivity
MDD vs. HCs	63.21	41.03	71.64	**67.92**	**89.55**	**30.77**	66.04	97.01	12.82
PTSD vs. HCs	67.78	68.63	66.67	**80.00**	**86.27**	**71.79**	75.56	88.24	58.97
PTSD vs. MDD	66.10	71.64	58.82	**70.34**	**74.51**	**67.16**	66.10	78.43	56.72
PTSDm vs. HCs	71.64	76.92	64.29	**82.09**	**85.71**	**79.49**	79.10	67.86	87.18
PTSDm vs. MDD	70.53	86.57	13.04	70.53	0.00	100.00	**71.58**	**50.00**	**80.60**
PTSDc vs. HCs	77.42	60.87	87.18	**82.26**	**73.91**	**87.18**	72.58	56.22	82.05
PTSDc vs. MDD	74.44	88.06	26.09	75.56	34.78	89.55	**76.67**	**34.78**	**91.04**

MDD: major depressive disorder; HCs: healthy controls; PTSD: post-traumatic stress disorder; PTSDm: PTSD-mono diagnosis; PTSDc: PTSD-comorbid diagnosis.

studies. According to positron emission tomography (PET) research, female PTSD patients with traumatic memory deficits showed decreased blood flow in the hippocampus, fusiform, and ITG during reading traumatic text in comparison with HCs (Bremner et al., 1999). Also, abnormal brain activations in PC, insular, cuneus, precuneus, and lingual gyrus were found during emotional cognitive processing (Shin et al., 2001). A few studies reported abnormal activities in the AC, amygdala, hippocampus and parietal area occurred during automatic information processing using oddball task (Bryant et al., 2005; Semple et al., 2000). Moreover, the abnormal middle frontal activation of PTSD is well-summarized (Hayes et al., 2012; Simmons and Matthews, 2012).

Most brain regions which showed altered brain activation in our results exceedingly coincided with the previous studies. That is, the abnormal brain activation in PTSD during attention processing may be associated with patients' traumatic memory or negative appraisal. Moreover, we found negative correlations between CSD and both BDI

and BAI. The result means that if the severities of depression and anxiety symptoms are worse in individuals with PTSD, the activity in five brain areas (fusiform gyrus, IOG, lingual gyrus, MOG, and PC) decrease. It might support that the altered source activities of PTSD during attention processing.

Also, the patients with PTSDc showed significant differences in both sensor- and source-level characteristics compared to MDD. However, the PTSDm showed significant differences only in P300 latency. In the present study, the patients with PTSDc tended to have severe anxiety symptom compared to PTSDm patients (31.38 ± 15.90 vs. 28.71 ± 15.75). The previous study has shown that the severe anxiety symptom of PTSD was closely related to declined P300 characteristics (Metzger et al., 1997). That is, the higher symptom of anxiety in PTSDc than PTSDm might have influenced the abnormal source activation during cognitive process.

4.3. Machine-learning-based classification between PTSD and MDD

Machine learning method was applied to classify patients and HCs using sensor- and source-level features extracted from P300 ERP data. Two classification pairs (PTSDm-MDD and PTSDc-MDD) showed maximum classification accuracies when both sensor- and source-level features were simultaneously used, while the other classification pairs (PTSD-HCs, MDD-HCs, PTSD-MDD, PTSDm-HCs, and PTSDc-HCs) showed maximum classification accuracies when only source-level features were used.

According to our results, the source-level features seem to play a more important role in classifying different groups of people compared to the sensor-level features. It is thought that source-level features could supplement the weaknesses of sensor-level features such as the low spatial resolution originating from volume conduction and contaminations from artifacts (Nolte et al., 2004; Nunez et al., 1997; van den Broek et al., 1998). Especially, the improved spatial information by the use of source imaging might contribute to the enhanced classification accuracy because some brain regions showed disease-specific dysfunctions. In the present study, the CSD in the cingulate gyrus showed PTSD-specific dysfunction and played an important role in discriminating PTSDs (PTSD, PTSDm, and PTSDc) from HCs and MDD (for more details on the selected features, please refer to the supplementary information). When maximum classification accuracy was achieved in classification pairs including PTSDs, the cingulate gyrus was always selected as the source-level features, with the activities in the cingulate gyrus being smaller in PTSDs than HCs and MDD. The cingulate gyrus is involved in several functioning such as emotion, memory, and pain (Rolls, 2015; Vogt, 2005). It is well-known that patients with PTSD suffer from traumatic memory (Herman, 1992; Rubin et al., 2008), and the mal-functioning of memory in PTSD is associated with the activation in cingulate gyrus (Sartory et al., 2013). Taken together, this may suggest that reduced activation in cingulate gyrus of PTSD is caused by traumatic events, and it could be used as an important factor when classifying PTSD from MDD in the present study.

Moreover, except the pair of MDD vs. HC, the sensitivities of classification were increased when using source-level features. In the diagnostic field, the value of sensitivity indicates the ability to classify the patients with specific disease as the same disease (Lalkhen and McCluskey, 2008). That is, in present study, the PTSD patients could be identified with PTSD with relatively higher sensitivities when using source-level features compared to sensor-level features. While, when identifying the patients with MDD, the performance of sensor-level feature is better than source-level features. This result may infer that the different types of features should be selected when diagnosing each different disorders.

4.4. Limitations

There are some limitations in the present study. First, all of the patients were on medication, we could not control for possible confounding effects of the psychotropic medication. Second, we did not use the individual head model for source imaging; thus, source activity in the deep brain such as amygdala could not be investigated. Third, we did not perform the three groups' comparison due to restriction of sLORETA software; thus, the differences of CSD among three groups (PTSD vs. MDD vs. HCs) could not be estimated. Fourth, we have tried to strictly exclude the anxiety disorder in our study; however, the influence of anxiety in diagnosis and results may be existed.

Despite shortcomings, our study is noteworthy because it is the first attempt to find the differences in P300 processing among PTSD, MDD, and HCs. Altered P300 features in both sensor and source-level were found in PTSD compared to MDD and HCs, also significant correlations between CSD and symptom severity scores were revealed. Moreover, we achieved acceptable classification accuracies using P300 features when discriminating different groups. These results suggest that

reduced amplitude and prolonged latency would reflect declined cognitive processing of PTSD, the reduced CSD and relationships with symptom scores would be supportive of impaired cognitive system in PTSD. Also, altered P300 features in both sensor- and source-level might be promising biomarkers to differentiate PTSD from HCs and MDD. To keep pace with the advances in technology, we're trying to improve our approach with deep-learning algorithms as a future direction.

Declaration of Competing Interest

The authors declare no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2019.102001.

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