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Functional connectivity of resting state EEG and symptom severity in patients with post-traumatic stress disorder

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ABSTRACT

Objectives: Post-traumatic stress disorder (PTSD) is thought to be a brain network disorder. This study aimed to examine the resting-state functional connectivity (FC) in patients with PTSD.
Methods: Thirty-three PTSD patients and 30 age- and gender-matched healthy controls were recruited. Symptom severity of the PTSD patients was assessed, and 62-channel EEG was measured. EEGs were recorded during the resting state, with the eyes closed. Three nodal network measures to assess nodal centrality [nodal degree (Dnodal; connection strength), nodal efficiency (Enodal; communication efficiency), and betweenness centrality (BC; connection centrality)] were calculated in the delta, theta, alpha, beta, and gamma bands.
Results: Dnodal and Enodal of the beta and gamma bands were decreased in PTSD patients compared to healthy controls. These decreased nodal centrality values were observed primarily at the frontocentral electrodes. In addition, Dnodal of the beta and gamma bands was significantly correlated with depressive symptoms and increased arousal symptoms, respectively. Enodal of the beta and gamma bands was significantly correlated with re-experience, increased arousal, and the severity and frequency of general PTSD symptoms.
Conclusion: Compared to controls, patients with PTSD were found to have decreased resting-state FC, and these FC measures were significantly correlated with PTSD symptom severity. Our results suggest that resting-state FC could be a useful biomarker for PTSD.

1. Introduction

Post-traumatic stress disorder (PTSD) is a debilitating anxiety condition that develops after encountering life-threatening mental trauma and is characterized by unremitting distressing re-experiencing of the traumatic event, avoidance, and hyperarousal, which are thought to be direct or indirect effects of altered memory processing. Several brain areas whose function may be altered in PTSD have been identified: the ventromedial prefrontal cortex (vmPFC), insula, amygdala, and hippocampus (Fonzo et al., 2010; Quirk and Mueller, 2008; Stevens et al., 2013). In a resting state MRI study, Sripada et al. (2012b) demonstrated that functional connectivity (FC) in a PTSD group was decreased in the rostral anterior cingulate cortex/vmPFC, and increased in the salience network including the amygdala. In sum, decreased ventromedial prefrontal cognitive control and increased hippocampal and limbic activation are considered to be the core of PTSD pathology.

EEG has been employed only in a small number of studies on PTSD to explore the differences in neural dynamics between patients and healthy controls. Kim et al. (2012) used non-linear analysis and found an increased nonlinear dynamic in the left hemisphere and decreased nonlinear dynamic in the right hemisphere in patients with PTSD. Cook et al. (2009) demonstrated that compared to control subjects, individuals who had experienced childhood trauma had significantly higher EEG coherence, suggesting that childhood psychological trauma may have a lasting impact on neuronal connectivity. Kemp et al. (2010) found that alpha activity in the right-parietotemporal region was enhanced in PTSD group compared to major depressive disorder group, and that right-frontal lateralization was positively correlated with PTSD symptom severity.

While previous EEG studies have reported abnormal brain dynamics for patients with PTSD, to date, no study has examined the large-scale FC network in the resting state to reveal the brain network of patients with PTSD. Recently, a growing number of studies have examined

Abbreviations: PTSD, post-traumatic stress disorder; FC, functional connectivity; EEG, electroencephalogram; Dnodal, nodal degree; Enodal, nodal efficiency; BC, betweenness centrality; ANOVA, analyses of variance; SCID, Structured Clinical Interview for DSM; SSRIs, selective serotonin reuptake inhibitors; MMPI, Minnesota Multiphasic Personality Inventory; DTS, Davidson Trauma Scale; SIP, Structured Interview for PTSD; BDI, Beck Depression Inventory; HAMD, Hamilton Depression Rating Scale, HAMA, Hamilton Anxiety Scale; MI, mutual information.

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resting-state FC using various modalities to investigate intrinsic brain activity. Many studies have reported the effects of various diseases on neural connectivity and networks (Bassett and Bullmore, 2009). FC networks have been studied with the aim of characterizing the differences between normal controls and patients with brain network diseases such as Alzheimer's disease, using MEG (Montez et al., 2009; Stam et al., 2009) or EEG (Stam et al., 2007), and schizophrenia, using MEG (Bassett et al., 2009) or EEG (Rubinov et al., 2009). Likewise, on the basis of the known abnormal brain dynamics in patients with PTSD (Cook et al., 2009; Kemp et al., 2010; Kim et al., 2012), we predicted that the brain of PTSD patients would show a different resting-state FC network than that of healthy controls; understanding these differences would increase our understanding of PTSD pathophysiology.

We hypothesized that patients with PTSD would show altered FC around the frontal and temporal areas and that the nodal network features of the resting state-FC network would be significantly correlated with PTSD symptom severity. To test our hypotheses, we evaluated the nodal features using centrality measures of the resting-state FC network of high-density EEG signals obtained from 33 patients with PTSD and 30 age- and gender-matched healthy controls. To the best of our knowledge, this is the first study to employ resting-state FC obtained using EEG for examining the changes that occur in PTSD.

2. Methods

2.1. Participants

Our study involved 33 patients with PTSD (mean age 37.6; 17 men) and 30 age- and gender-matched healthy control subjects (mean age 34.1 years; 16 men), who were recruited from the Psychiatry Department of Inje University Ilsan Paik Hospital. All the patients had developed PTSD after experiencing motor vehicle accidents, and were diagnosed using the Structured Clinical Interview for DSM, 4th edition (SCID) Axis I Psychiatric Disorders (First et al., 1997). Out of 33 patients with PTSD, 28 were taking antidepressants: 17 were taking selective serotonin reuptake inhibitors (SSRIs); 5, venlafaxine; 3, mirtazapine; 2, duloxetine; and 1, bupropion. Twenty-nine patients were taking benzodiazepine: 13 were taking lorazepam; 12, clonazepam; 2, alprazolam; and 2, diazepam.

Healthy controls were recruited from the local community through local newspapers and posters. During screening, the controls were evaluated using the SCID Axis I Psychiatric Disorders (First et al., 1997) and received a physical examination. All participants had no history of major trauma such as a serious car accident, combat experience, sexual assault, serious physical injury etc. Additionally, they were not taking medications with potentially psychoactive effects. They also completed the Minnesota Multiphasic Personality Inventory (MMPI) (Kim, 1996). Only those with MMPI scores falling within the normal range were included in the study. Exclusion criteria included the presence of any identifiable psychiatric or neurological disorder, hearing impairment, head injury, personal history of psychiatric disease, family history of psychiatric illness, mental retardation, alcohol or substance abuse, and any 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 for other precise motor skills. After being informed of the details of the study, all subjects provided their written informed consent prior to participation.

The study protocol was approved by the Institutional Review Board of Inje University Ilsan Paik Hospital. The demographics of the two groups are provided in Table 1; there were no significant group differences with regard to gender distribution, or age, except for a difference in education.

2.2. Psychological measurements

The Davidson Trauma Scale (DTS) and Structured Interview for PTSD (SIP) were administered to the patients with PTSD. DTS and SIP have been standardized for the 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 SSRIs in patients with PTSD symptoms (Davidson et al., 2002). It is a 17-item self-reported questionnaire that scores the severity and frequency of PTSD symptoms on a 5-point Likert-type scale. The DTS is simple to administer and takes less than 10 min. It has been administered in a variety of populations, including men and women with different traumata. The Korean version of the 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 following 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 the 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), Hamilton Depression Rating Scale (HAMD) (Hamilton, 1960), and Hamilton Anxiety Scale (HAMA) (Hamilton, 1959).

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

	PTSD ($n = 33$)	Healthy controls ($n = 30$)			
	Mean (SD)	Mean (SD)	t (χ^2)	df	p
Age (years)	37.64 (14.69)	34.07 (12.60)	1.03	61	0.307
Sex (male: female)	16:17	14:16	0.021*	1	0.85
Education (years)	12.39 (2.39)	13.83 (2.95)	−2.11	61	0.041
K-DTS	84.94 (20.21)				
K-SIP	42.00 (9.57)				
BDI	27.85 (12.16)				
HAMD	20.45 (8.38)				
HAMA	24.70 (9.00)				

Note: *, χ^2; PTSD, posttraumatic stress disorder; DTS, Davidson Trauma scale; SIP, Structured Interview for PTSD; BDI, Beck Depression Inventory; HAMD, Hamilton Depression Rating Scale; HAMA, Hamilton Anxiety Rating Scale.

2.3. EEG acquisition and preprocessing

EEG signals were recorded using a NeuroScan SynAmps amplifier (Compumedics, El Paso, TX) from 62 surface 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) mounted on a Quick Cap, using a modified 10–20 placement scheme. The ground electrode was placed on the forehead, and the reference electrodes were located at the Cz electrode. The vertical electrooculogram (EOG) was recorded using two electrodes: one located above and one located below the right eye. The horizontal EOG was recorded at the outer canthus of each eye. The electrode impedance was less than 5 kΩ.

Signals from all channels were amplified, filtered (DC-100 Hz), and digitized with a sampling frequency of 1 kHz. Resting-state EEGs were recorded for 5 min with the eyes closed. Gross movement artifacts were removed from the recorded data by visual inspection, and epochs (epoch length 2.048 s) for each subject were obtained. Epochs were rejected if they included significant physiological artifacts (amplitude exceeding ± 75 μV) at all cortical electrode sites. Finally, 15 artifact-free epochs (epoch length 2.048 s) were obtained for each subject, in order to calculate mutual information (MI) and allow further network analysis.

2.4. Estimation of functional connectivity

MI, which quantifies the shared information between two time series based on information theory, was employed as a measure of FC between EEG channels in the five frequency bands corresponding to the classical EEG bands: delta (1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz), and gamma (30–50 Hz). MI has been used as the measure of coupling between two time series and information flow to evaluate brain connectivity in both EEG and MEG (Alonso et al., 2010; Caballero-Gaudes et al., 2013; Jeong et al., 2001; Jin et al., 2010, 2011a,b,c, 2012). We used weighted graphs defined by MI without thresholding.

We estimated MI values of the band-pass filtered time series to create an association matrix between EEG channels. MI was calculated using the following equation:

$$\mathrm{MI} = \mathrm{MI}XY = \mathrm{MI}YX = \mathrm{MI}(X(t), Y(t)) = -\frac{1}{2}\log 2(1-a2)$$

where, a is the correlation coefficient between the two time series $X(t)$ and $Y(t)$. Here, we assumed the two time series $X(t)$ and $Y(t)$ are Gaussian distributed functions. This equation is referred to as the linearized information flow between the two signals and considers only second moments in the data (Nichols et al., 2006). MI matrices of each epoch and frequency band were calculated, and then, 15 MI matrices were averaged for the following estimation of graph theoretic measures.

2.5. Nodal centrality measures

For FC network analysis, weighted and undirected graphs from the MI matrix were evaluated. Binary graphs can indicate the existence of connections, while weighted graphs can be used to indicate the strength of connections (Reijneveld et al., 2007). According to previous studies (Barrat et al., 2004; Barthelemy et al., 2005; Newman, 2004; Onnela et al., 2005; Park et al., 2004; Stam et al., 2009), weighted graphs can be more accurate models of real networks.

Basically, N is the set of all nodes, and n is the number of nodes. The total number of nodes was 62, corresponding to the number of EEG channels. The links between two nodes, i and j, are associated with the connection weights, w_{ij}. The weights were normalized by the maximum value of the MI matrix so as to produce $0 \le w_{ij} \le 1$ for all nodes (Rubinov and Sporns, 2010). The shortest weighted path length of the path from node i to node j, the so called di,jw, was calculated as $\sum_{wst \in g_{i\to j}^{w}} f(wst)$, where f is an inverse from the weight to length, and $gi \to jw$ is the shortest weighted path between the two nodes i and j (Rubinov and Sporns, 2010).

Nodal network properties were assessed using three centrality measures: nodal degree (Dnodal), nodal efficiency (Enodal), and betweenness centrality (BC). Dnodal indicates the total weight connected to a node, reflecting the strength of the connection represented at a node. It was calculated at each node i, as $\sum_{j \in N} wij$ with the connection weights w_{ij}.

Enodal can be defined as the inverse of the harmonic mean of the shortest path length between a node i and all other nodes in a network (Achard and Bullmore, 2007). It is regarded as a measure of the communication efficiency (Wang et al., 2009). It is derived from the following equation:

$$\mathrm{Enodal}\ (i) = \frac{1}{n-1}\sum_{j\in N, j\neq i}\frac{1}{d_{i,j}^{w}}$$

BC is defined as the fraction of all of the shortest paths in the network that pass through a given node (Rubinov and Sporns, 2010). Thus, it measures how often nodes occur on the shortest paths between other nodes (Buckner et al., 2009). It is defined by the following equation: $\mathrm{BC} = \sum_{\substack{h,j\in N \\ h\neq j, h\neq i, j\neq i}} \frac{ghj(i)}{ghj}$, where ghj is the number of shortest paths between node h and j, and $ghj(i)$ is the number of shortest paths between node h and j passing through i. BC is normalized by the mean value of BCs in a network (He et al., 2008; Wang et al., 2010); later, we denote it as normBC.

Extraction of the shortest path length from a weight matrix and calculation of each nodal network metrics were performed using functions from the Brain Connectivity Toolbox (http://www.brain-connectivity-toolbox.net/).

2.6. Statistical analysis

Normality of the nodal network measures was graphically assessed. If the data are normal, the plot should be linear. The data had a normal distribution (Fig. S1). A two-sample t-test was performed to detect statistical intergroup differences in each nodal centrality for each frequency band. The significance level was applied after a Bonferroni correction ($p < 0.05/N = 0.00086, N = 62$). Pearson's correlation coefficients were evaluated in order to investigate the relationship between the nodal measures and symptom severity as a clinical variable.

All statistical analysis was performed using Statistics Toolbox in MATLAB.

2.7. Visualization

Pajek software (http://pajek.imfm.si/doku.php) was employed for the network visualization of the functional connectivity network. To present the data, the group-averaged, normalized MI matrices at each band were thresholded by the mean + SD value of all the subjects. The thresholding was done only for the visualization. Otherwise, the network would not be recognizable due to too many connections. The scalp plotting program used in the present study, "headplot" in MATLAB script, was adapted from Delorme et al. (2007).

3. Results

FC network differences between the healthy controls and PTSD patients at each frequency band are shown in Fig. 1. Different FC networks between the healthy controls and PTSD patients were observed. It is noticeable that less connections over the anterior brain region in the PTSD patients group in the beta and gamma frequency bands.

3.1. Nodal network measures

3.1.1. Dnodal centrality

In the beta frequency band, the Dnodal value of FCz was greater in healthy controls than in patients with PTSD [FCz, 0.056(0.003) vs. 0.041(0.002), $t = 3.936$, $df = 61$, $p = 0.0002$]. In the gamma frequency band, the Dnodal values of AF4, FC1, FC2, FC4, and C1 were greater in healthy controls than in patients with PTSD [AF3, 0.077(0.006) vs. 0.051(0.004), $t = 3.616$, $df = 61$, $p = 0.0006$; FC1, 0.068(0.006) vs. 0.045(0.003), $t = 3.671$, $df = 61$, $p = 0.0005$; FC2, 0.073(0.006) vs. 0.049(0.003), $t = 3.600$, $df = 61$, $p = 0.0006$; FC4, 0.078(0.007) vs. 0.051(0.004), $t = 3.786$, $df = 61$, $p = 0.0004$; C1, 0.064(0.007) vs. 0.038(0.003), $t = 3.600$, $df = 61$, $p = 0.0006$]. Fig. 2 illustrates the electrodes showing significant differences between the two groups at each frequency band.

3.1.2. Enodal centrality

In the beta frequency band, the Enodal values of FC4 and C1 were greater in healthy controls than in patients with PTSD [FC4, 0.919(0.019) vs. 0.803(0.025), $t = 3.711$, $df = 61$, $p = 0.0004$; C1, 0.767(0.029) vs. 0.630(0.023), $t = 3.718$, $df = 61$, $p = 0.0004$]. In the gamma frequency band, the Enodal values of FC6 and C1 were greater in healthy controls than in patients with PTSD [FC6, 0.958(0.030) vs. 0.812(0.028), $t = 3.626$, $df = 61$, $p = 0.0006$; C1, 0.824(0.032) vs. 0.676(0.026), $t = 3.623$, $df = 61$, $p = 0.0006$]. Fig. 2 illustrates the

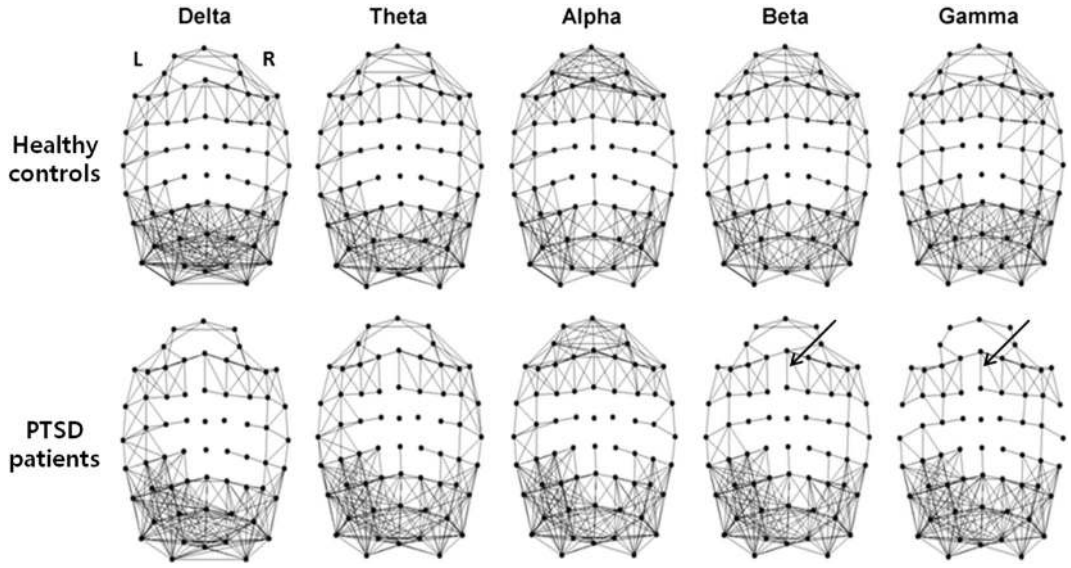

Fig. 1. Graphical representations of functional connectivity (FC) network in healthy controls and PTSD patients at each frequency band. Grand-averaged MI matrices at each frequency were thresholded by a mean + SD MI value of all the nodes across the subjects. Upper row shows the FC networks in the healthy controls, and lower row indicates the FC networks in the PTSD patients (L, left side; R, right side). Arrows mean less connections over the anterior brain region in the PTSD patients group in the beta and gamma frequency bands.

electrodes showing significant differences between the two groups at each frequency band.

3.1.3. normBC centrality

There were no significant differences in normBC between healthy controls and patients with PTSD.

3.2. Correlation between symptom severity and centrality

3.2.1. Dnodal centrality

In the beta frequency band, the Dnodal of FCz was significantly correlated with the HAMD score ($r = -0.384$, $p = 0.028$). In the gamma frequency band, the Dnodal of FC2 was significantly correlated with the score for SIP-increased arousal ($r = 0.379$, $p = 0.030$). Fig. 3 illustrates the scattergrams showing the significant correlations between the Dnodal centralities and clinical variables.

3.2.2. Enodal centrality

In the beta frequency band, the Enodal of FC4 was significantly correlated with the scores for SIP-re-experience ($r = -0.433$, $p = 0.012$). The Enodal of C1 was significantly correlated with the scores for SIP-total ($r = -0.421$, $p = 0.015$), SIP-re-experience ($r = -0.401$, $p = 0.021$), SIP-increased arousal ($r = -0.379$, $p = 0.030$), DTS-total ($r = -0.381$, $p = 0.029$), and DTS-frequency ($r = -0.417$, $p = 0.016$). In the gamma frequency band, the Enodal of C1 was significantly correlated with the scores for DTS-total ($r = -0.504$, $p = 0.003$), DTS-frequency ($r = -0.505$, $p = 0.003$), and DTS-severity ($r = -0.475$, $p = 0.005$). Fig. 3 illustrates the scattergrams showing the significant correlations between the Enodal centralities and clinical variables.

4. Discussion

Our study revealed that patients with PTSD have alterations in the resting-state brain FC network. Our main findings are that patients

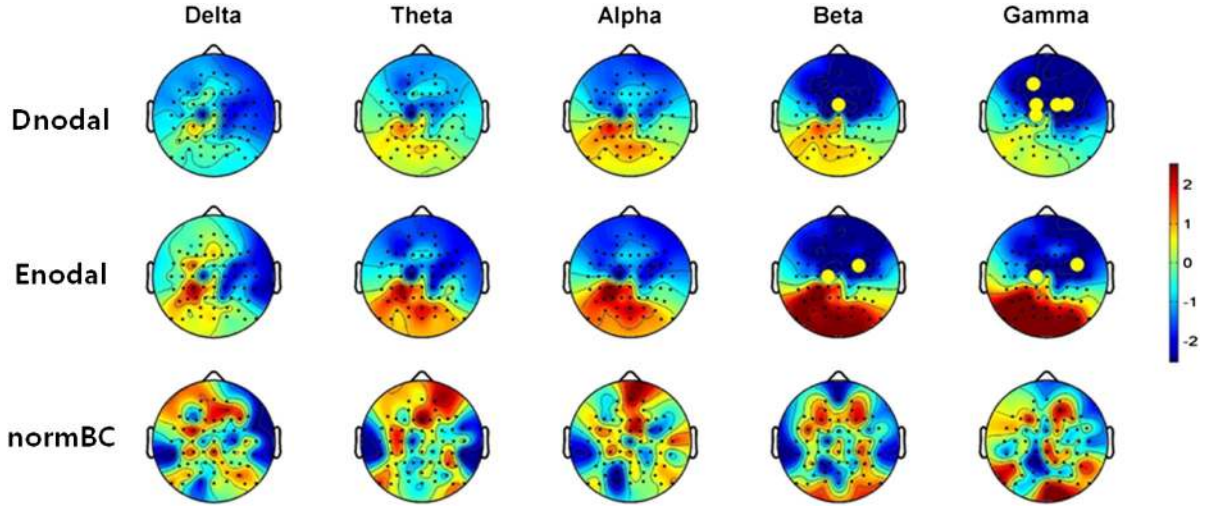

Fig. 2. T-maps showing intergroup differences in each nodal centrality at each frequency band. Yellow dots correspond to the locations, which have shown significantly decreased values for patients with PTSD compared to healthy controls (Dnodal: FCz for the beta band and AF3, FC1, FC2, FC4, and C1 for the gamma band; Enodal: FC4z and C1 for the beta band, and C1 and FC6 for the gamma band). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

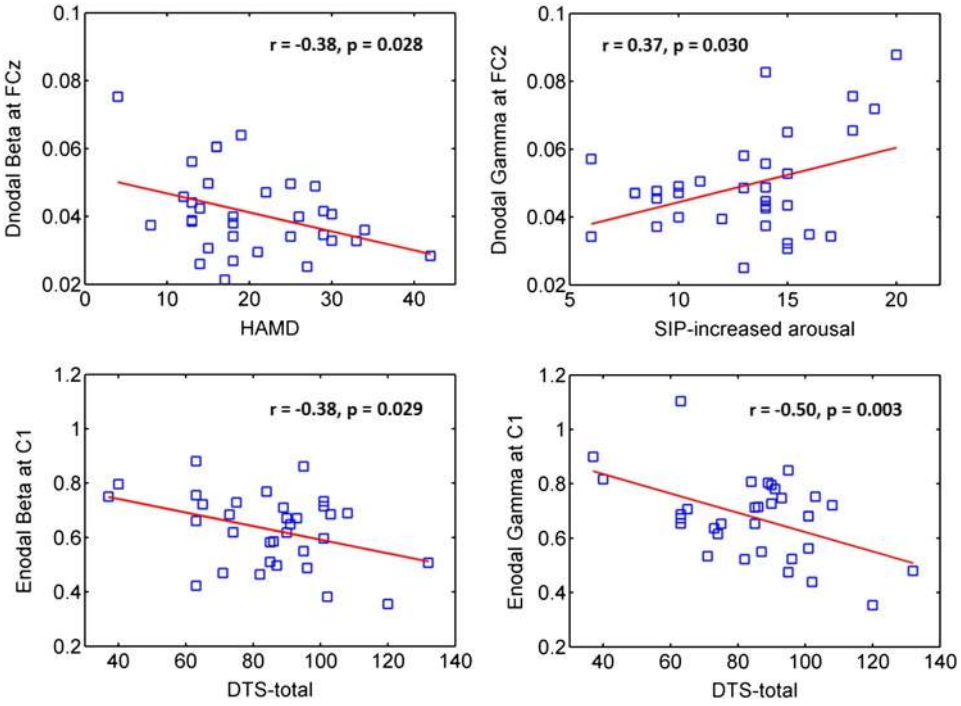

Fig. 3. Scattergrams showing the significant correlations between Enodal and Dnodal centralities and clinical variables. DTS-total: Davidson Trauma Scale—total score, HAMD: Hamilton Depression Scale, SIP: Structured Interview for PTSD.

with PTSD have decreased FC in terms of connection strength and efficiency over the frontocentral electrodes, and these FC metrics were significantly correlated with PTSD symptom severity.

In the present study, FC of the frontal region was decreased in patients with PTSD compared to healthy controls. This finding is thought to reflect frontal lobe dysfunction in patients with PTSD, which has been consistently reported. However, not all regions of the frontal cortex play the same role in patients with PTSD. The dorsal anterior cingulate (dACC) appears to be hyperactive in PTSD (Milad et al., 2009), whereas the vmPFC is often observed to be hypoactive and shows decreased connectivity with medial temporal structures (Sripada et al., 2012a,b; Stevens et al., 2013). In particular, two brain areas—the amygdala and the vmPFC—have been proposed as key regions with alterations in patients with PTSD (Myers-Schulz and Koenigs, 2012). In patients with PTSD, a defect in functioning of the vmPFC, which exerts inhibitory control over the amygdala, impairs amygdala inhibition, resulting in unchecked amygdala activity and pathological distress (Rauch et al., 2006; Shin et al., 2006).

Furthermore, we found decreased FC only in the higher frequency bands: beta and gamma. Because the beta and gamma bands are believed to be involved with higher cognitive functions (Holschneider and Leuchter, 1995; Lee et al., 2010; Moon and Lee, 2011), the FC at these high-frequency bands could indicate the higher cognitive information flow. Furthermore, previous qEEG studies (Begic et al., 2001; Ehlers et al., 2006) have revealed that patients with PTSD have increased beta and gamma band activity over the frontal regions and suggested that these altered high-frequency activities are indicative of pathological cortical hyper-excitability in these patients. Cook et al. (2009) reported that compared to controls subjects, adults with a history of childhood trauma have higher alpha and beta band coherence over the right centrotemporoparietal area. Generally, coherence tends to be higher in individuals with earlier traumas. Taken together, these results suggest that the frontal region of patients with PTSD might be in a hyper-excitable state with increased coherence; however, there is low regional connectivity in the functional state. The hyper-excitability and low regional connectivity seem contradictive in the pathophysiology of patients with PTSD. However, it can be hypothesized that the frontal hyper-excitability of the brains of PTSD patients has low efficiency in controlling the subcortical limbic regions because of its low FC.

In addition, in the present study, decreased FC was found in the Dnodal and Enodal metrics for the frontocentral electrodes. Dnodal and Enodal indicate the total strength of the connection represented at a node and the communication efficiency, respectively. Therefore, our results suggest that compared to healthy controls, patients with PTSD have weaker connection strength and communication efficiency in the frontocentral regions. In addition, efficiency as a network measure can be used to investigate the adaptive functional reorganization based on the economical properties of the brain networks (Achard and Bullmore, 2007; Jin et al., 2012; Kitzbichler et al., 2011). Thus, decreased Enodal metrics in the frontocentral regions may be related to the adaptive reorganization of the resting-state FC network in patients with PTSD, due to the traumatic experience. This decreased communication efficiency would reflect a defect in frontal inhibitory control over the amygdala, resulting in amygdala activation. In future studies, the concept of adaptive reorganization should be examined with a longitudinal follow-up design.

A number of studies have reported decreased FC of the default mode network in patients with PTSD; however, these studies used fMRI with limited temporal resolution. Sripada et al. (2012a) demonstrated decreased FC of the default mode network in the rostral anterior cingulate cortex/vmPFC of patients with PTSD. Bluhm et al. (2009) reported that their PTSD group exhibited particularly diminished levels of connectivity between the posterior cingulated cortex seed region and the right frontal region as well as the left thalamus. There are also conflicting fMRI reports that have shown increased frontal activation in the resting-state following a life threatening traumatic event (Qin et al., 2012; Yin et al., 2011, 2012). However, these PTSD studies did not recruit healthy controls as a control group, making it difficult to compare their results with those of other, which were contrasted with healthy controls. Possibly, the different modalities of fMRI and EEG, as well as different characteristics of the patients with PTSD and control subjects might have contributed to the inconsistent results. fMRI can investigate brain dynamics of very limited frequency bands under 1 Hz. However, in the present EEG study, we found the altered nodal centralities in

resting-state FC in both the beta and gamma band. Further EEG studies are required to properly examine high-frequency brain dynamics in patients with PTSD.

We found significant correlations between the Dnodal and Enodal metrics and symptom severity of PTSD patients; the metrics showed significant negative correlations with DTS, SIP, and HAMD scores. In this vein, communication efficiency at the central region showed a negative correlation with SIPS-increased arousal symptoms. However, there was a significant positive correlation between SIPS-increased arousal and connection strength at the frontal region in the gamma frequency. These divergent correlations could reflect functional differences between frontal and central regions. Furthermore, these findings suggest that the connection strength (Dnodal) and communication efficiency (Enodal) are not in the same direction in the hyper-arousal symptom of patients with PTSD.

This is similar to the results of Bae et al. (2011), who reported that SIP-increased arousal score was positively correlated with P300 source activity in the frontal areas, while SIP-avoidance and numbing were negatively correlated this source activity in patients with PTSD. In addition, Begic et al. (2001) suggested that the increased beta activity in patients with PTSD is related to cortical hyperexcitability, prolonged wakefulness, or attention disturbances. In the present study, the symptom-dependent disparate correlations seem to be reflecting the diverse pathophysiological change in the brain of patients with PTSD.

In summary, our results suggest that PTSD symptom severity and depressive symptoms are related with a decrease in FC, while increased arousal is related with increased FC in the frontal lobe.

Our study has a number of limitations. Firstly, all patients with PTSD were taking psychotropic medications. Therefore, we could not rule out potential medication effects in this study. Secondly, we analyzed only the cortical level FC. It is difficult to infer any sub-cortical abnormality from the cortical level analysis. Despite these limitations, our results have their strengths because this is the first EEG resting-state analysis in patients with PTSD. Our results suggest that EEG could be a useful tool for connectivity analysis, and further research is highly recommended for a spectrum of psychiatric illnesses.

In conclusion, compared to healthy controls, patients with PTSD have decreased Dnodal and Enodal values in the resting-state FC network at frontocentral electrodes, in the beta and gamma bands. These nodal network measures, representing connection strength and communication efficiency, were significantly correlated with symptom severity in patients with PTSD. Our results suggest that nodal network features of the FC network in the resting-state EEG could prove to be a useful biomarker for PTSD.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.pnpbp.2014.01.008.

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