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Hemispheric asymmetry in non-linear interdependence of EEG in post-traumatic stress disorder

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Aim: While volumetric and metabolic imaging on post-traumatic stress disorder (PTSD) patients has been intensively performed, few studies using electro-encephalograms (EEG) have been done as yet. The aim of the present study was to investigate abnormalities in functional connectivity of cortical networks in PTSD.

Methods: Non-linear interdependence (NI), a measure of bidirectional, non-linear information transmission between two time series, was used. Resting EEG were recorded for 18 PTSD patients and 18 sex-matched healthy subjects on 16 channels with their eyes closed.

Results: The NI patterns in PTSD patients were hemisphere asymmetric: an increase in NI in the fronto-parieto-temporal regions of the left hemisphere (F7, F3, T3, C3, T5 and P3) and a decrease in the fronto-parieto-occipital regions of the right hemisphere (F4, C4, P4 and O2). The non-linearity of NI in EEG, estimated from the surrogate data method, exhibited an increase in the PTSD patients as compared with that of healthy subjects, particularly in the left hemispheric cortex.

Conclusion: Abnormal functional connectivity in PTSD can be assessed using NI, a measure of multi-channel EEG.

Key words: asymmetry, electroencephalogram, non-linear interdependence, post-traumatic stress disorder.

P OST-TRAUMATIC STRESS DISORDER (PTSD) is a psychiatric disorder that may develop after an extremely traumatic psychological event such as combat experience, car accidents or sexual abuse. The major PTSD symptoms include loss of memory, recurrent intrusive thoughts or images, excessively high levels of anxiety, depression, and nightmares. Thus, PTSD patients re-experience the life-threatening events through repeated memories, dreams, flashbacks and/or exposure to a similar situation. It is reported that approximately 3.5% of adults aged ≥18 years – approximately 7.7 million people in the USA – suffer from PTSD.[1]

Many studies have now shown the seriousness of PTSD and demonstrated physiological etiologies in the cerebra of those suffering from PTSD. For example, there have been extensive studies showing volumetric and metabolic alterations in the brains of PTSD patients, particularly in the hippocampus and the anterior cingulate gyrus.[2–9] These studies reported a decrease in hippocampal volume.[2–4,10] Also, studies on metabolic rates have reported decreased *N*-acetylaspartate/creatine (NAA/Cr) ratio and increased choline/creatine (Cho/Cr) ratio in the bilateral hippocampus, as well as reductions in the NAA/Cr ratio in the anterior cingulate gyrus.[8,9]

A few spatiotemporal dynamic studies on PTSD have been performed. EEG analysis of PTSD patients recently indicated diverse features: increased theta activity over the central regions, increased beta activity over the frontal, central and left occipital regions,[11] decreased alpha power in overall regions,[12] and increased gamma activity in the frontal region.[13] Functional connectivity studies using coherence measures on PTSD are even less common. Metzger *et al.* found increased right-sided parietal activation in association with PTSD arousal symptoms.[14] Enhanced right anterior and posterior activation has also been reported in PTSD patients.[15]

Although abnormalities of functional connectivity have been found in patients with PTSD, the connection regions and properties are not consistent across the experiments and analyses. In addition, most of the studies on functional connectivity are based on volumetric and metabolic imaging of PTSD patients, but few studies have been done using electroencephalograms (EEG). Recently, our group showed that the dimensional complexity of the EEG in PTSD patients was lower than that of normal individuals, indicating that PTSD patients have globally reduced complexity in their EEG waveforms.[16] This suggests that PTSD patients might exhibit abnormal functional integrations, because the dimensional complexity of the EEG reflects the functional integration between different cortical regions.

Therefore, the primary aim of the present study was to investigate abnormalities in functional connectivity of cortical networks in PTSD based on the EEG. The specific aims of the present study were (i) to assess if there is any abnormality in functional connectivity among different cortical regions in PTSD patients compared with normal subjects; (ii) to estimate the non-linearity in functional connectivity in PTSD; and (iii) to measure the direction of information transmission between different cortical regions in PTSD in a resting state condition using non-linear interdependence (NI).

Several non-linear multivariate measures for EEG have been proposed and used to quantify non-linear information transmission among cortical regions such as mutual information, phase synchronization, and NI. While cross-correlation measures linear dependence between two time series, these non-linear measures also estimate both linear and non-linear dependence between two time series. The non-linear measures have been applied to the EEG in patients with neuropsychiatric disorders. They have shown abnormalities in non-linear information transmission among cortical regions, which cannot be detected by linear measures such as cross-correlation. Mutual information has been applied, as a non-linear information transmission measure, to EEG in Alzheimer's disease and has demonstrated reduced information transmission among interhemispheric regions.[17] Mutual information has also been applied to the EEG in schizophrenia[18] and in sleep deprivation.[19] Synchronization likelihood, another non-linear measure, was also applied to EEG in mild cognition impairment (MCI) and Alzheimer's disease,[20-24] epileptic seizures[25,26] and schizophrenia.[27] They showed abnormal information flow patterns in these disorders.

Particularly, NI is a significant measure of the degree of both linear and non-linear information transmission between two time series. In addition, NI is capable of providing information as to the direction of information flow between two regions that generate time series.[28] NI has been used to investigate the relationships between EEG signals recorded from epileptogenic areas, and has identified the proper spatiotemporal organization of the seizures of medial temporal lobe origin.[29] A dysregulation in the organization of dynamic interactions across supra-regional brain systems was found in schizophrenia, including larger concurrent clusters of NI across the scalp, and stronger disturbance in left intrahemispheric coupling.[30]

METHODS

Subjects and EEG recording

All PTSD patients and normal controls were recruited from the Program for PTSD at St Mary's Hospital, Catholic University of Korea. PTSD patients fulfilled the relevant PTSD DSM-IV diagnosis criteria, having recorded a total severe score of ≥50 on the Clinician-Administered PTSD Scale, and had undergone various investigations including clinical history, physical and neurological examination, routine laboratory tests, electrocardiogram, EEG and structural brain magnetic resonance imaging. Detailed clinical information on the present PTSD patients is provided in a previous study.[16] All subjects signed written informed consent approved by the local Institutional Review Board prior to participation.

Eighteen PTSD patients were recruited (10 men, eight women; mean age, 36.9 ± 9.2 years) who were

Table 1. Subject data

Variables	PTSD ($n = 18$)	Control ($n = 18$)	Significance
Gender			
Male	10	12	NS
Female	8	6	
Age (years)	36.9 ± 9.2	26.8 ± 4.2	NS
Time from traumatic event (years)	6.1 ± 2.3		
Trauma type			
Motor vehicle accident	19		
Physical or sexual assault	4		
Witness injury or death	3		
CAPS-2 total score	76.2 ± 12.1		

CAPS-2, Clinician-Administered Post-traumatic Stress Disorder (PTSD) Scale Part 2.

all on stable psychopharmacological regimens of either selective serotonin re-uptake inhibitors (paroxetine, $n = 12$; fluoxetine, $n = 11$) or serotonin/norepinephrine re-uptake inhibitors (venlafaxine, $n = 4$). Six of them were on ongoing benzodiazepine (alprazolam) treatment. They underwent 2 weeks of drug washout before EEG recording (16.2 ± 1.3 days; range, 15–19 days).

Eighteen normal control subjects (12 men, six women; mean age, 26.8 ± 4.2 years) were recruited in the same hospital through local advertisements. Both PTSD patients and normal control subjects were right-handed. Exclusion criteria included a history of another Axis I psychiatric disorder, psychotropic medication usage within the past 2 weeks, head trauma with loss of consciousness, and/or a systemic illness or other neurological illness that could account for cognitive impairment (Table 1).

The EEG were recorded from 16 scalp locations using the international 10–20 system, from the subjects in a relaxed state with eyes closed. Potentials from the 16 channels referenced against linked earlobes were amplified on a San-Ei EE1121 amplifier (San Ei Electric, Osaka, Japan) using a time constant of 0.1 s. Overall amplification was 20 000-fold. After 82 s of continuous EEG recording were acquired at 400 Hz, we digitized this using a 12-bit analog-digital converter on an IBM personal computer. EEG segments containing noise from swallowing, sweating, eye movements detected with electrooculography, or body movements detected using electromyography, were excluded from analysis. All EEG data were processed using a digital Butterworth IIR bandpass filter with cut-off frequencies of 0.5 and 60 Hz for the resting condition to reduce movement artifacts. Prin-

cipal component analysis (PCA) was also applied to reduce the noise possibly present in the EEG recording prior to data analysis. The stationarity of the EEG were visually analyzed, and contaminated ones were excluded for further analysis. After the visual inspection of EEG stability, we removed those lacking stability for ≥30 s. The general quality of the EEG data used for the present analysis, the profile of the EEG power spectra across all frequencies and the profile of the complexity were examined in the previous study.[16]

Non-linear interdependence analysis

Non-linear interdependence estimates the linear and non-linear information flow from one time series (X) to the other (Y), which is a measure of how well one time series (X) predicts the other (Y). The method we used to evaluate NI between two EEG recordings is a slightly modified version of the algorithm proposed by Terry and Breakspear.[31]

To assess how well one time series (X) predicts the other (Y), we used statistical measurement.[32] First, we normalized each time series with the average and standard deviation of each time series. We reconstructed the normalized time series into a trajectory in a multidimensional phase with embedding dimension m and time delay L. For the value of the time delay L in the embedding procedure, the first local minimum of the average mutual information between the set of measurement X(t) and X(t + L) is often used, which ranged from 16 to 50 ms in the present study. Mutual information measures linear and non-linear dependence of two variables. The choice of the time lag and the embedding dimension

should be very cautious, because an inappropriate setting for the time lag and the embedding dimension may lead to spurious results, particularly for a finite number of data. In principle, the embedding dimension should be chosen such that it is much larger than the expected dimensional complexity $(D2)^2 + 1$. Most non-linear dynamic studies on physiological data, however, used 3–20 as an embedding dimension because of the limited number of data points. We used optimal embedding dimension methods to find a suitable embedding dimension using the Kennel method, which results in 3–10 as an embedding dimension.[33,34] We also reproduced the results of testing the algorithm in the previous study using NI.[35]

In this trajectory, at each time point, t, we assigned points to represent this time point, x_t and y_t. To determine the relationship, we compared aspects of their neighborhood points. There were *2m* number of the nearest points around x_t, called nearest neighborhood and annotated as $x_{nn(t)}$. For each point in state space, *2m* number of vertices was chosen to contain x_t in its volume and to minimize the size of the simplex. Next, we took the points in Y that had the same time point of nn(t), annotated as $y_{nn(t)}$. We calculated the center of mass of the simplex made out of *2m* $y_{nn(t)}$. That center of mass y_{com} is the point predicted by X. Thus, the difference between y_t and y_{com} shows how well X predicts Y. To normalize, we divided $|y_t - y_{com}|$ by $|y_t - y_{rand}|$, where y_{rand} is the center of mass of the simplex that is made out of *2m* random combinations of points in Y. The value calculated in this way is called the prediction error. If $y_{nn'(t)}$ and $y_{nn(t)}$ are close (i.e. if there is strong NI), the prediction error will be near 0. Conversely, if there is a weak or no NI, the prediction error will reach 1.

To determine the indepth information flow, we applied the concept of forward time step. We did the same evaluation using nn(t) + H (forward time step) of X, and nn'(t + H) of Y, for H = 1,2,3, . . . , 20. This whole process was carried out for all the time points t and between all the combinations of time series with the order considered, that is, 16 by 16 for each subject.

First, we constructed two time series each from two different systems, *X(t)* and *Y(t)*, and normalized each time series of length N,

$$\widehat{X_i(t)} = \frac{X_i(t) - \langle X_i(t) \rangle}{\sigma_{Xi}}, \ \widehat{Y_i(t)} = \frac{Y_i(t) - \langle Y_i(t) \rangle}{\sigma_{Yi}} \quad (1)$$

where $\langle \ \rangle$ indicates the time average and σ the standard deviation of each time series, $i = 1,2, . . . , N$. We then reconstructed the normalized time series with the embedding dimension m and time delay L of each time series in state space in $t = 1,2, . . . , N - \max[(m-1)L, (m-1)L]$, as follows:

$$\mathbf{x}(t) = \left(\hat{X}(t), \hat{X}(t+L), \hat{X}(t+2L), ... , \hat{X}(t+(m-1)L) \right), \quad (2)$$

$$\mathbf{y}(t) = \left(\hat{Y}(t), \hat{Y}(t+L), \hat{Y}(t+2L), ... , \hat{Y}(t+(m-1)L) \right). \quad (3)$$

At certain time t_i and a given reference point at that time point x(t_i), we determined a simplex consisting of *2m* vertices in state space X. We chose *2m* points that satisfy the following 2 conditions: (i) they are the nearest neighborhood of x(t_i); and (ii) they should enclose the reference point x(t_i). To check whether the vertices enclosed the reference point x(t_i), we calculated a simplex center for x(t_i) according to the weighted average of the vertices as

$$x_{cm}(t_i) = \frac{\sum_{k=1}^{2m_1} \left(|x(t_{ik}) - x(t_i)| \right)^{-1} \times x(t_{ik})}{\sum_{k=1}^{2m_1} \left(|x(t_{ik}) - x(t_i)| \right)^{-1}}. \quad (4)$$

Eventually, the nearest point of the center of the simplex was replaced as a new reference point x(t_r), $r = 1,2 . . . , N$, in X. Thus, at time t_r, the 2m vertices in the simplex of the newly chosen reference point x(t_r) enclosed the new reference point x(t_r) and so were determined to minimize the size of the simplex.

The predicted vector y(t_r) by the vector x(t_r) was calculated by the average of the weighted distances between x(t_r) and each vertex y(t_{rk}) in the simplex in Y, $k = 1,2, . . . , 2m$. We obtained the prediction vector $y_{predicted}(t_r)$ at time t_r in Y on X by

$$y_{predicted}(t_n) = \frac{\sum_{k=1}^{2m_1} w_{rk} \times y(t_{rk})}{\sum_{k=1}^{2m_1} w_{rk}} \left(w_{nk} : \text{weight factor}; w_{nk} \right) \quad (5)$$

$$= \left(|x(t_{rk}) - x(t_r)| \right)^{-1}.$$

Thus, the prediction error $\varepsilon_{y(x)}(t_r)$ was the difference between the predicted vector $y_{predicted}(t_r)$ and actual vector y(t_r) in Y,

$$\varepsilon_{y(x)} = |\gamma_{predicted}(t_r) - \gamma(t_r)|. \tag{6}$$

To normalize the prediction error, we chose a random reference point $x_{rand}(t_r)$ in X and calculated the prediction vector $y_{rand}(t_r)$ following the above algorithm. The prediction error $\varepsilon_{rand}(t_r)$ was estimated by the difference between the predicted vector $y_{rand}(t_r)$ and the actual vector $y(t_r)$ as following:

$$\varepsilon_{rand} = |\gamma_{rand}(t_r) - \gamma(t_r)| \tag{7}$$

Therefore, the normalized prediction error of $y(t)$ as predicted by $x(t)$ was determined by the ratio $\langle \varepsilon_{y(x)} \rangle_{rms}$ to $\langle \varepsilon_{rand} \rangle_{rms}$ as the following equation,

$$\nabla_{y(x)} = \frac{\langle \varepsilon_{y(x)} \rangle_{rms}}{\langle \varepsilon_{rand} \rangle_{rms}} \tag{8}$$

where $\langle \ \rangle_{rms}$ denotes the root mean square.

We estimated the prediction error $\nabla_{x(y)}^{H}$ between the actual $\gamma(t_r)$ and predicted $\gamma_{predicted}(t_r)$ in Y as predicted by $x(t)$ in X at iterated H future time steps with the equation,

$$\nabla_{y(x)}^{H} = \frac{\langle \varepsilon_{y(x)}^{H} \rangle_{rms}}{\langle \varepsilon_{rand}^{H} \rangle_{rms}}. \tag{9}$$

Terry and Breakspear improved the original version devised by Schiff *et al.*[31] The Terry and Breakspear version produces a simplex that contains the reference point and is the smallest in volume, instead of simply taking some nearest points in the original version. Another difference is that, in the prediction error calculation, they used a random combination as the denominator to normalize the prediction error, instead of using the mean error.

The main difference between the present method and the Terry and Breakspear version lies in the method of epoch selection. While Terry and Breakspear took epochs of every 2.048 s out of 130 s and compared all the co-occurrences between them, we took one 5-s epoch among six selected 5-s segments in which all the 16 EEG recordings were stationary, and then calculated NI among all pairs. The main reason why we modified the method is because not all epochs were stationary. Some of the EEG data did not contain a stationary 5-s duration that could be extracted. It is assumed that a 5-s segment contains all the typical features of the PTSD subject, and that different time segmentation methods should not affect the results. This 5-s segment selection significantly reduced computational labor without loss of

primary information, and it also ruled out the problem of window selection. These methods are thus applied to all the 5-s segments used in the present study.

Surrogate data analysis of the prediction error

To study the non-linearity of the interdependence in two EEG, the prediction errors of their surrogate data were compared with those of the original EEG data. The surrogate data consisted of randomly shuffled data from the original data but their power spectrum was preserved to eliminate any non-linear deterministic components of the original data. Using the TISEAN program, 19 surrogate data sets for each subject were generated. The mutual non-linear interdependency algorithm described in the previous section was applied to the constructed surrogate data. The average $\langle \nabla_{surr}^{H} \rangle$ and the standard deviation σ_{surr}^{H} of the future prediction errors in $H = 0,1,2,\ldots,20$ for the surrogate data sets were calculated. To evaluate the non-linearity, the z-score for the future prediction error ∇_{exp}^{H} from the experimental data was calculated for each time series of the EEG channels. $\left(\left| \frac{\langle \nabla_{surr}^{H} \rangle - \nabla_{exp}^{H}}{\sigma_{surr}^{H}} \right| \right)$ The z-score presents the degree of non-linearity between the two time series. A small z-score indicates the linear stochastic relationship of the time series, and as the z-score grows, the dependence between the systems becomes more non-linearly deterministic.

RESULTS

We calculated NI for 256 pairs of EEG for each subject, including 20 forward steps, with 18 subjects in each group. Figure 1 presents prediction errors for each pair of EEG with directionality in normal controls and in PTSD patients, with $P < 0.05$ for H = 0, 5, and 10. Figure 1 shows the hemispheric asymmetry: better prediction for PTSD patients on the left hemisphere regions and better prediction for normal controls on the right-side regions. This result indicates increased non-linear interactions in the left hemispheric regions and decreased non-linear interactions in the right hemisphere regions in PTSD patients. Interactions with significant difference are mainly within one side of the hemisphere, with some exceptions such as T3 to P4
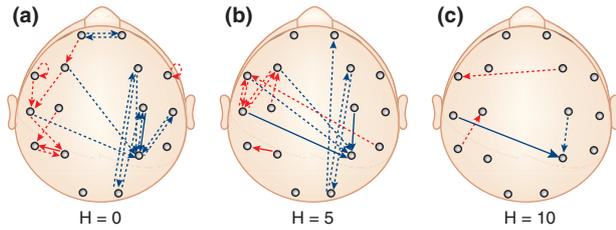
Figure 1. Prediction error pattern. Red arrows, significantly decreased prediction error (i.e. increased functional connectivity) in post-traumatic stress disorder (PTSD) patients; blue arrows, significantly increased prediction error (i.e. decreased functional connectivity) in PTSD patients. (- - -) $P < 0.05$; (—) $P < 0.01$.

(H = 0, 5, 10 and 15), Fp1 to Fp2 and Fp2 to Fp1 (H = 0), F3 to P4 (H = 0 and 5), F7 to P4 (H = 5), T6 to F7 (H = 5), F4 to F7 (H = 10) and F3 to Fp2 (H = 20). In other words, this finding indicates increased left hemisphere regional connectivity and decreased right hemisphere regional connectivity in PTSD patients. Particularly, prediction error for P4 was significantly reduced in PTSD patients at approximately four nearby channels.

Significant differences in the left hemisphere between the two groups were fronto-parieto-temporal regions (F7, F3, T3, C3, T5 and P3; increased NI in PTSD patients), and those in the right hemisphere were fronto-parieto-occipital regions (F4, C4, P4 and O2; decreased NI in PTSD patients). In particular, P4 was significantly less predictable by C4 in PTSD subjects ($P < 0.001$ for H = 0 and 5, uncorrected) compared with controls, which persisted along the forward time steps H = 0–20 (Figure 2). Prediction error for T5 by P3 in PTSD subjects was significantly lower ($P < 0.001$ for H = 0 and 5, uncorrected) than that in controls. The number of interactions with significant differences in 'self-prediction' increased as H rises (C3, P3 and O2 at H = 15, F4, C3, C4, P3, P4 and O2 at H = 20). Some prominent differences are shown in Figure 2 with the whole forward step scale (H = 0–20). Bonferroni correction, however, did not produce significant differences in prediction errors for different H values between the two groups (Table 2).

We performed surrogate data analysis to investigate how much non-linearity is present in the information transmission among cortical regions in PTSD. We reconstructed 19 surrogate data sets with linear properties remaining from original EEG data, and then evaluated z from the formula $\left| \dfrac{\langle \nabla_{surr}^H \rangle - \nabla_{exp}^H}{\sigma_{surr}^H} \right|$. Z-values >2.326 were collected for
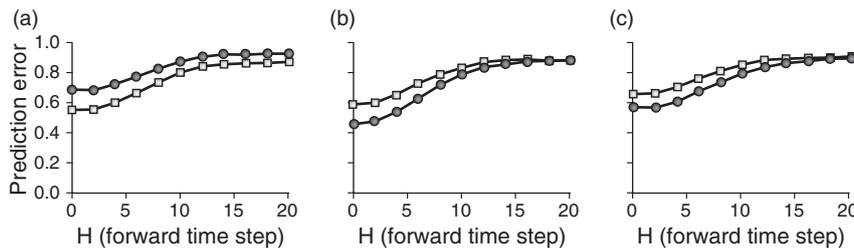

Figure 2. Changes in prediction error as H increases for a post-traumatic stress disorder (PTSD) patient for (a) C4 → P4 (b) P3 → T5 and (c) T3 → F3, respectively. (□) Control; (●) PTSD.

Table 2. Statistically significant prediction errors ($P < 0.01$)

X	→	Y	Control	PTSD patients	Control – PTSD	P	H
P3		T5	0.5967	0.4625	0.1342	0.0051	0
C4		P4	0.5557	0.6958	−0.1401	0.0010	0
P3		T5	0.6778	0.5841	0.0937	0.0096	5
C4		P4	0.6628	0.7535	−0.0907	0.0083	5
T3		P4	0.8854	0.9289	−0.0435	0.0033	5
T3		P4	0.9178	0.9452	−0.0274	0.0054	10

Prediction error <0, better prediction in normal controls; prediction error >0, better prediction in PTSD patients. X → Y, prediction error relates to prediction of Y by X.
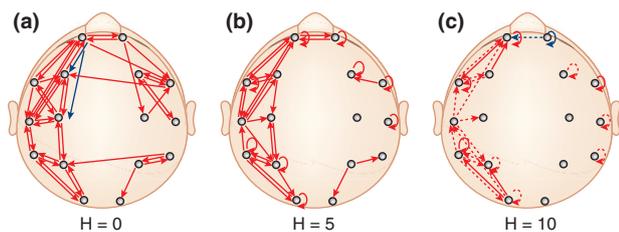H, Hurst exponent; PTSD, post-traumatic stress disorder.

Figure 3. Differences in z between electroencephalograms (EEG) in post-traumatic stress disorder (PTSD) patients and controls. Red arrows, relations with larger z in PTSD patients; blue arrows, relations with larger z in controls. Larger z means more non-linearity in information transmission. (- - -) $z > 2.326$ for either PTSD patients or controls (95% confidence); (—) $z > 3.090$ for either PTSD patients or controls (99% confidence). (For simplicity, only $z > 3.09$ are shown for H = 0 and 5).

95% confidence. Figure 3 shows interactions when either the PTSD patient group or the normal control group had $z > 2.326$ (only values of $z > 3.09$ are shown for H = 0 and 5; $z > 2.326$ represents 95% confidence and that larger than 3.09 represents 99% confidence), and z differences between the two groups. Red arrows indicate increase in z and blue arrows indicate decrease in z in PTSD patients.

The PTSD patients had $z > 2.326$ at all pairs of channels, with a few exceptions at the prefrontal regions (Fp1 and Fp2). This indicates that non-linearity is increased in the PTSD brain. Z-values also showed that there was a hemispheric asymmetry, in that there were more non-linear interactions in the left hemisphere compared with those on the right side. This indicates an increase in non-linearity in information transmission among cortical regions in PTSD patients compared with those of controls, particularly in the left hemisphere.

DISCUSSION

We applied NI methods to the EEG recordings of PTSD patients used in our previous study of the same subject groups aimed at evaluating their cortical complexity, in order to examine the origin of the EEG complexity.[16] To our knowledge, the current study is the first report on NI of multi-channel EEG in PTSD patients. We investigated the amount and direction of functional connectivity (i.e. the NI among all pairs of EEG) in PTSD and compared them with those of

healthy subjects. We found increased non-linear interdependency in the fronto-parieto-temporal regions of the left hemisphere and decreased non-linear interdependency in the fronto-parieto-occipital regions of the right hemisphere in PTSD patients compared with healthy subjects, increased non-linearity in information transmission particularly in the left hemisphere in PTSD patients, and different patterns of directional information flows between the two groups. These together suggest abnormal, hemisphere-asymmetric functional connectivity or information flow in PTSD patients.

There are a few reasons why we used NI to analyze the EEG of PTSD patients in this non-linear functional connectivity analysis. First, there have been a few previous studies investigating the linear dependence of different cortical regions (i.e. linear functional connectivity) using coherence of multi-channel EEG for PTSD patients, but the results were not consistent. Thus, we speculate that this discrepancy possibly arises from non-linear functional interactions among different cortical regions. Second, in our previous study, we found that the non-linear dimensional complexity of individual EEG in PTSD patients showed abnormality compared with that of normal individuals. We hypothesized that this abnormal non-linear property of the EEG is possibly associated with non-linear interactions among cortical regions, thus we can detect abnormal functional connectivity in PTSD brains using NI. Finally, the NI can detect the directionality of the information flow among cortical regions (i.e. between channels), which cannot be assessed using linear measures such as coherence. Thus, the NI was used to quantify directional information flows in the cerebral cortex of PTSD patients.

We speculate that the hemispheric asymmetry in functional connectivity in PTSD patients found in the present study is associated with a decrease in the hippocampal volumes in both hemispheres,[2,4] but with more decrease in the right hemisphere.[3] Furthermore, anterior cingulate volume was found to be decreased in only the right hemisphere of PTSD.[10] Reduced creatine-containing compounds were found in the right hippocampus of PTSD patients.[8] These hemispheric asymmetries in cortical/subcortical volumes and metabolism in PTSD might affect hemispheric asymmetry in functional connectivity. We should note, however, that hemispheric asymmetry in hippocampus of PTSD is still controversial, and the results equivocal. Some studies using structural

neuroimaging methods reported that hippocampal volume reduction of PTSD was found in both hemispheres, with even more significant decrease in the left[36] or in both hemispheres without significant asymmetry,[5,37] or found no significant asymmetry in both right and left hippocampi.[8] Anterior cingulate volume in PTSD was also reported to be decreased in both hemispheres without asymmetry.[7] In addition, studies on metabolic rates reported decreased NAA/Cr ratio and increased Cho/Cr ratio in the bilateral hippocampus, reductions in NAA/Cr ratio in the anterior cingulate gyrus[6] and reduced NAA in both hippocampi.[8,9] Thus, we suggest that the presence of abnormality in structure and function of the hippocampus and related areas may be associated with hemispheric asymmetry of non-linear information transmission among cortical regions in PTSD.

Quantitative EEG (qEEG) analyses have recently identified distinctive characteristics in PTSD patients compared with healthy subjects. Sleep EEG analysis showed decreased low-frequency EEG spectral powers during non-rapid-eye-movement (REM) sleep and increased beta power in REM versus non-REM sleep.[38] A marked decrease in delta power was also found during sleep and metyrapone-induced sleep.[39,40] EEG analysis of PTSD patients during waking states also produced diverse results. PTSD patients exhibited an increase in the theta activity over the central regions, an increase in beta 1 activity over the frontal, central and left occipital regions, an increase in beta 2 activity over the frontal regions,[11] a decrease in alpha power and an increase in beta power in overall regions,[12] and an increase in gamma activity in the frontal region.[13] qEEG analysis of PTSD patients performing during one-back working memory task showed reduced alpha power and an increased theta/alpha ratio, which are correlated with clinical and physiological measures.[41] Previous EEG frequency analysis did not show any hemispheric asymmetry, but abnormalities were found mostly in the frontal areas. Thus, we speculate that disturbed functional connections from frontal areas might be associated with hemispheric asymmetry in functional connectivity of NI.

More recently, functional connectivity studies using coherence measure on PTSD reported increased right-sided parietal activation in association with PTSD arousal symptoms.[14] EEG reactivity to eye opening was found to be correlated with left parieto-temporal delta frequency,[42] and increased relative left frontal activation was found to be correlated with post-traumatic growth.[43] Enhanced right anterior and posterior activations were also reported in PTSD patients.[15] This discrepancy might result from different frequencies for the coherence in the analysis and the different patient clinical conditions in the studies. In addition, patient trauma was different. In contrast, the present study is consistent with that by Arikan *et al.*[42] and Rabe *et al.*,[43] but not with that by Metzger *et al.*.[14] We speculate that this might arise from a discrepancy between linear and non-linear information transmission measures or different subject groups.

In our previous study, we found reduced dynamic complexity in EEG of PTSD patients, particularly right fronto-temporal regions.[16] Reduced dynamic complexity of the EEG indicates the availability of fewer state variables and degrees of freedom that generate the neural dynamics underlying PTSD symptoms or reduced functional integration among different cortical regions, which results in an overly rigid or constrained processing of information. The present result suggests that reduced dynamic complexity of EEG in right fronto-temporal regions of PTSD patients possibly arises from reduced non-linear information transmission and reduced non-linearity among cortical regions in PTSD patients.

We should note that there were limitations in this study, such as the relatively small sample size, the absence of detailed psychometric data, and inclusion of a heterogeneous subject group having a wide range of illness severity and traumatic etiologies. Particularly, the possible effects of medication should be noted. Many drugs are known to induce EEG changes.[44] In order to reduce the effect of drugs, only patients who did not have any drug therapy for 2 weeks were included in this study. Furthermore, we should examine EEG in PTSD patients that are recorded during the performance of cognitive tasks to investigate the role of functional connectivity in PTSD.

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