

Dimensional complexity of the EEG in patients with posttraumatic stress disorder

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Abstract

Recent electrophysiological studies have reported evidence of information processing abnormalities in patients with posttraumatic stress disorder (PTSD). The aim of this study is to examine dynamical complexity of the EEG in PTSD patients, which is thought to reflect information processing of the brain. Resting EEG recordings (32 800 data points acquired continuously from 82 s of an EEG record) were obtained in 16 channels of 27 patients with PTSD from a mixed civilian trauma population and 14 healthy subjects. The correlation dimension (D_2) of the EEG was used to quantify the complexity of the cortical dynamics underlying the EEG signal. The PTSD patients were found to have lower D_2 values than those of the healthy subjects in most channels (Fp1, F8, C4, P4, T3, T4, T5, T6, and O1), indicating that PTSD patients have globally reduced complexity in their EEG waveforms. This study supports the hypotheses that PTSD patients exhibit disturbed cortical information processing, and that non-linear dynamical analysis of the EEG can be a tool for detecting changes in neurodynamics of the brain in PTSD.

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1. Introduction

Since the introduction of diagnostic criteria for posttraumatic stress disorder (PTSD) in 1980, several lines of investigation have suggested the presence of cognitive disturbances in persons who

meet diagnostic criteria for PTSD (Yehuda, 1998). Several event-related potential (ERP) studies have reported abnormalities in the ERP waveform (McFarlane et al., 1993; Charles et al., 1995; Attias et al., 1996; Bleich et al., 1996; Metzger et al., 1997; Gillette et al., 1997). Behavioral studies have also suggested the presence of deficits in the monitoring and regulation of mnemonic material in PTSD patients (Yehuda et al., 1995). Taken

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together, these findings suggest the presence of abnormalities in higher-order information processing of individuals who have PTSD.

There are only a few EEG studies of PTSD patients. Wolf et al. (1988) examined the EEG activity in sleep and waking states of PTSD patients to find that all EEG findings (sleep and awake) were within normal limits. Recently, Begic et al. (2001) using conventional spectral methods found that PTSD patients had increased theta activity over central regions and increased beta activity over frontal, central and left occipital regions.

Nonlinear dynamical measures, such as the correlation dimension (D_2), entropy, and the first positive Lyapunov exponent (L_1), have previously been used to quantify complexity of information processing across a variety of experimental and biological systems. The D_2 is defined as the number of independent variables that are necessary to describe the behavior of a dynamical system. However, since the EEG reflects cortical dynamics, the D_2 of the EEG is often interpreted as a measure of complexity (or flexibility) of information processing of the brain. The neurophysiological meaning of the complexity is not clear. However, the complexity can be interpreted as the integration of information in the brain. This includes both the integration of the activity of functionally segregated neuronal groups and the integration of incoming stimuli with ongoing, spontaneous brain activity (Tononi et al., 1998).

Decreased D_2 values of the EEG have been detected in a variety of clinical conditions. Clinical and experimental conditions characterized by decreased D_2 values seem to have in common the presence of grossly impaired information processing, such as Creutzfeld–Jacob disease (Babloyantz and Destexhe, 1987), epilepsy (Frank et al., 1990; Lehnertz and Elger, 1998), Alzheimer's disease (Pritchard et al., 1994; Besthorn et al., 1995; Stam et al., 1996; Jeong et al., 1998c, 2001b), Parkinson's disease (Stam et al., 1994, 1995), schizophrenia (Jeong et al., 1998b; Kim et al., 2000), and sleep deprivation (Jeong et al., 2001a). In addition, EEG complexity, as measured by D_2 over the central and posterior cortex, was higher while subjects solved tasks of divergent (creative) than

convergent thinking, which in turn was higher than D_2 values during mental relaxation (Molle et al., 1999). These findings suggest that the D_2 of the EEG may serve as quantitative index of CNS information processing.

The aim of the present study is to examine CNS information processing of PTSD patients using a complexity measure and the surrogate data method, and to find out whether PTSD patients exhibit changes in the nonlinear structure of the EEG. We estimated D_2 values of the EEG in PTSD patients and compared them with those of healthy subjects. In this study, we regarded the D_2 as a measure of complexity to quantify the degree of complex behavior of the brain rather than as an absolute measure to distinguish between deterministic and stochastic dynamics.

2. Methods

2.1. Subjects

The subjects were recruited from the Program for PTSD at St. Mary's Hospital, The Catholic University of Korea, and diagnosed according to DSM-IV criteria (American Psychiatric Association, 1994) on the basis of the Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Edition (SCID-I-PE) (First et al., 1998). Subjects with a total severity score of at least 50 (range 0–136) on the Clinician Administered PTSD Scale, Part 2 (CAPS-2) were enrolled (Weathers and Litz, 1994). All patients had undergone a thorough evaluation that included clinical history, physical and neurological examination, routine laboratory tests, electrocardiogram, EEG, and a structural brain magnetic resonance imaging scan. Twenty-seven subjects (13 men, 14 women; age: 39.5 ± 8.6 years) were finally enrolled.

At the time of the enrollment, subjects were all on stable psychopharmacological regimens of either selective serotonin reuptake inhibitors (paroxetine = 12, fluoxetine = 11) or serotonin/norepinephrine reuptake inhibitors (venlafaxine = 4). Six patients were ongoing benzodiazepine (alprazolam) treatment. The EEG was recorded after a drug washout period of 2 weeks (16.2 ± 1.3 days, range: 15–19) to reduce the influence of

drugs as much as possible. Fourteen age- and sex-matched healthy control subjects (7 men, 7 women; 34.2 ± 6.3 years) were recruited through local advertisements.

All PTSD and control subjects were right-handed as assessed by the Neurological Evaluation Scale-Korean Version; Chae, 1994). 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, or a systemic illness or other neurological illness that could account for the cognitive impairment. All subjects signed a written informed consent approved by the local Institutional Review Board prior to participation.

2.2. EEG recording

EEGs were recorded from 16 scalp locations (F7, T3, Fp1, F3, C3, P3, O1, F8, T4, T5, T6, Fp2, F4, C4, P4, and O2) of the international 10–20 system. With the subjects in a relaxed state and eyes closed, 82 s of continuous EEG recording (32 780 data points at a sampling frequency of 400 Hz) were acquired and digitized using a 12-bit analog–digital converter on an IBM personal computer. Recordings were made under the eyes-closed condition to obtain as many stationary EEG data points as possible. Although it was inevitable to include mild blinking artifacts during the sampling periods, epochs contaminated by artifacts on visual inspection were excluded from the study. Potentials from the 16 channels referenced against linked earlobes were amplified on a San-Ei EE1121 machine using a time constant of 0.1 s. Overall amplification was 20 000-fold. Each EEG record was judged to be free from electrooculographic and movement artifacts and to contain minimal electromyographic (EMG) activity.

2.3. Data analysis

We first transformed a one-dimensional time series into a trajectory in a multidimensional phase space. The concept of phase space is central to nonlinear dynamical analyses. In a hypothetical system described by n state variables, the phase space is n -dimensional. Each state of the system

corresponds to a point in the phase space whose n coordinates are the values of the state variables for this specific state. If the system is observed through time, the sequence of points in phase space forms a dynamical trajectory. This trajectory fills a subspace of the phase space and is called the system's attractor.

Reconstruction of the attractor in phase space is performed with the technique of plotting delay coordinates. Let an observed time series $x_j(t)$ be the output of a differentiable dynamical system f on an m -dimensional manifold M . In order to unfold the projection back to a multivariate phase space that is a representation of the original system, we use the delay coordinates $y(t) = [x_j(t), x_j(t+T), \dots, x_j(t+(d-1)T)]$ from a single time series $x_j(t)$ after performing an embedding procedure. $y(t)$ is one point of the trajectory in the phase space at time t , $x(t+iT)$ are the coordinates in the phase space corresponding to the time-delayed values of the time series, T is the time delay between the points of the time series considered, and d is the embedding dimension. Takens (1981) showed that an attractor reconstructed by using delay coordinates from a single time series x_j and by performing an embedding procedure is topologically equivalent to the original system.

The choice of an appropriate time delay T and embedding dimension d is important for the success of reconstructing the attractor with finite data. We used the first local minimum of the average mutual information between the sets of measurement $x(t)$ and $x(t+T)$ for the time delay T (Fraser and Swinney, 1986).

We estimated the minimum embedding dimension in the reconstruction procedure using an algorithm proposed by Kennel et al. (1992) to obtain a proper embedding dimension for the EEG. The algorithm is based on the idea that in the passage from dimension d to dimension $d+1$, one can differentiate between points on the orbit that are true neighbors and those that are false. A false neighbor is a point in the data set that is identified as a neighbor solely because we are viewing the orbit (the attractor) in too small an embedding space ($d < d_{\min}$). When we have achieved a large enough embedding space ($d \geq d_{\min}$), all neighbors of every orbit point in the multivariate phase space

will be true neighbors. The detailed algorithm was described by Jeong et al. (1998a)

The dimensional complexity (D_2) determines the number of independent variables that are necessary to describe the dynamics of the original system. D_2 is a measure of complexity of the process being investigated and characterizes the distribution of points in the phase space. The larger the D_2 of the attractor, the more complicated the behavior of the system.

The Grassberger–Procaccia algorithm (GPA) was used to calculate the D_2 of the EEG attractors (Grassberger and Procaccia, 1983). D_2 determination is based on calculating the relative number of pairs of points in the phase-space set that are separated by a distance less than r . It is computed as

$$D_2 = \lim_{r \rightarrow 0} \lim_{N \rightarrow \infty} \frac{\log C(r, N)}{\log r} \quad (1)$$

where the correlation integral $C(N, r)$ is defined by

$$C(r) = \frac{1}{N^2} \sum_{\substack{i,j=1 \\ i \neq j}}^N \theta(r - |\vec{y}_i - \vec{y}_j|) \quad (2)$$

in which y_i and y_j are the points of the trajectory in the phase space, N is the number of data points in the phase space, the distance r is a radius around each reference point y_i and θ is the Heaviside function, defined as 0 if $x < 0$, and 1 if $x \geq 0$. For small r , a scaling property is exhibited: $C(N, 1) \propto r^{D_2}$. For a self-similar (fractal) attractor, the local scaling exponent is constant, and this region is called a scaling region. This scaling exponent can be used as an estimate of the correlation dimension. If one plots $C(N, r)$ vs. r on a log–log scale, the correlation dimension is given by the slope of the $\log C(r)$ vs. $\log r$ curve over a selected range of r , and the slope of this curve in the scaling region is estimated by least-squares fitting. The detailed algorithm is presented by Jeong et al. (1998a, 2001a).

The Theiler correction (Theiler, 1986) was used to exclude pairs of points that are close, not

because of the attractor geometry but just because they are temporally correlated. We used the time at which the autocorrelation function has decayed to $1/e$ as the correlation time for the Theiler correction.

The surrogate data analysis was also performed to test whether the EEG is nonlinear or not. The surrogate data were constructed by phase randomization of the original EEG signals. In this way, surrogate data are produced whose linear properties, such as power spectrum and histogram, are unchanged, whereas nonlinear properties that may be present are destroyed. Statistical differences of nonlinear measures (the D_2 in this study) between the original data and their surrogate data indicate the presence of nonlinear structure in the original data. The detailed algorithm for generating the surrogate data is presented by Schreiber and Schmitz (2000).

2.4. Statistical analyses

D_2 s for each group were expressed as means \pm S.D. Analysis of variance (ANOVA) for repeated measures using ‘group’ and ‘leads’ as factors was performed. As a post hoc analysis, Student’s unpaired t -test was used to analyze the group differences in D_2 between PTSD patients and control subjects at each channel (SPSS 9.0 for Windows). A P -value < 0.05 was considered significant.

3. Results

As designed, demographic data of the patient group were not different from those of the control group (Table 1). Subjects’ index trauma occurred 6.6 ± 2.8 years prior to the time point of enrollment. The most common trauma types represented were motor vehicle accidents ($N=20$, 74%), physical or sexual assaults ($N=4$, 15%), and witness injury or death ($N=3$, 11%).

Time delays of 18–56 ms were used for the embedding procedure in all the subjects. An embedding dimension $d=15$ was used for this procedure, because the estimation of the minimum embedding dimension proposed 15 as an optimal value of the embedding dimension. All the EEG

Table 1
Demographic and clinical data

Variables	PTSD (<i>N</i> = 27)	Control (<i>N</i> = 14)	Significance
Gender			
Male	13	7	NS
Female	14	7	
Age (years)			
Mean (S.D.)	39.5 (8.6)	34.2 (6.3)	NS
Time from traumatic event (years)			
Mean (S.D.)	6.6 (2.8)		
Trauma types			
Motor vehicle accident	20		
Physical or sexual assault	4		
Witness injury or death	3		
Total scores on the CAPS-2	76.5 (12.7)		

CAPS-2 indicates Clinician Administered Posttraumatic Stress Disorder (PTSD) Scale Part 2.

signals had a clear plateau, the scaling region, in the log $C(r)$ vs. log r graph.

First of all, we used the surrogate data method to assess whether the EEG obtained in the present study had a nonlinear structure. In both groups, we found significant differences of D_2 values between the raw EEG data and their surrogate data in all channels ($P < 0.001$), indicating the presence of nonlinear structure within the EEG (Fig. 1). The differences of D_2 values between the raw and surrogate EEG data were approximately 0.6–1.2, which is not significantly different in either group of subjects. This result confirms the validity of the application of nonlinear dynamical methods to the EEG used in this study.

The average D_2 values from 16 channels and their standard deviations between PTSD patients and control subjects are summarized in Table 2. There were significant main group effects between PTSD and control subjects ($F = 24.6$, d.f. = 1, $P < 0.001$). There were also significant 'lead' effects ($F = 2.9$, d.f. = 15, $P < 0.001$) and a lead \times group interaction ($F = 2.2$, d.f. = 15, $P = 0.005$). Post hoc analysis showed that the PTSD patients had significantly lower D_2 values than control subjects in the Fp1 ($P = 0.017$), F8 ($P < 0.001$), C4 ($P = 0.014$), P4 ($P = 0.001$), T3 ($P < 0.001$), T4 ($P = 0.001$), T5 ($P < 0.001$), T6 ($P = 0.008$), and O1 ($P = 0.005$) leads. The average D_2 values at other

channels in the PTSD patients also tended to be lower than those in the control subjects, although these did not reach the level of statistical significance (Fig. 2). There were no significant correlations between clinical measures derived from the CAPS-2 and the average D_2 values in all EEG channels. In addition, the time lags (T) were not correlated with D_2 values in either the PTSD or the control group.

4. Discussion

The development of nonlinear analyses has heralded a new era in the study of neural dynamics, and it is being increasingly applied to the study of numerous features of the brain (McKenna et al., 1994). Assuming that EEG signals reflect underlying neural processing, nonlinear analysis of the EEG may help to investigate dynamical properties of information processing through the underlying neural systems that generate EEG potentials (Molle et al., 1999). A host of studies have now raised the possibility that nonlinear analysis of the EEG may be a useful tool in differentiating normal and pathological brain states (Micheloyannis et al., 1998; Jeong et al., 1998b,c, 2001a,b; Jeong, 2002). The present study demonstrates that patients with PTSD have decreased D_2 values, or less complex dynamics, in most channels of their EEGs com-

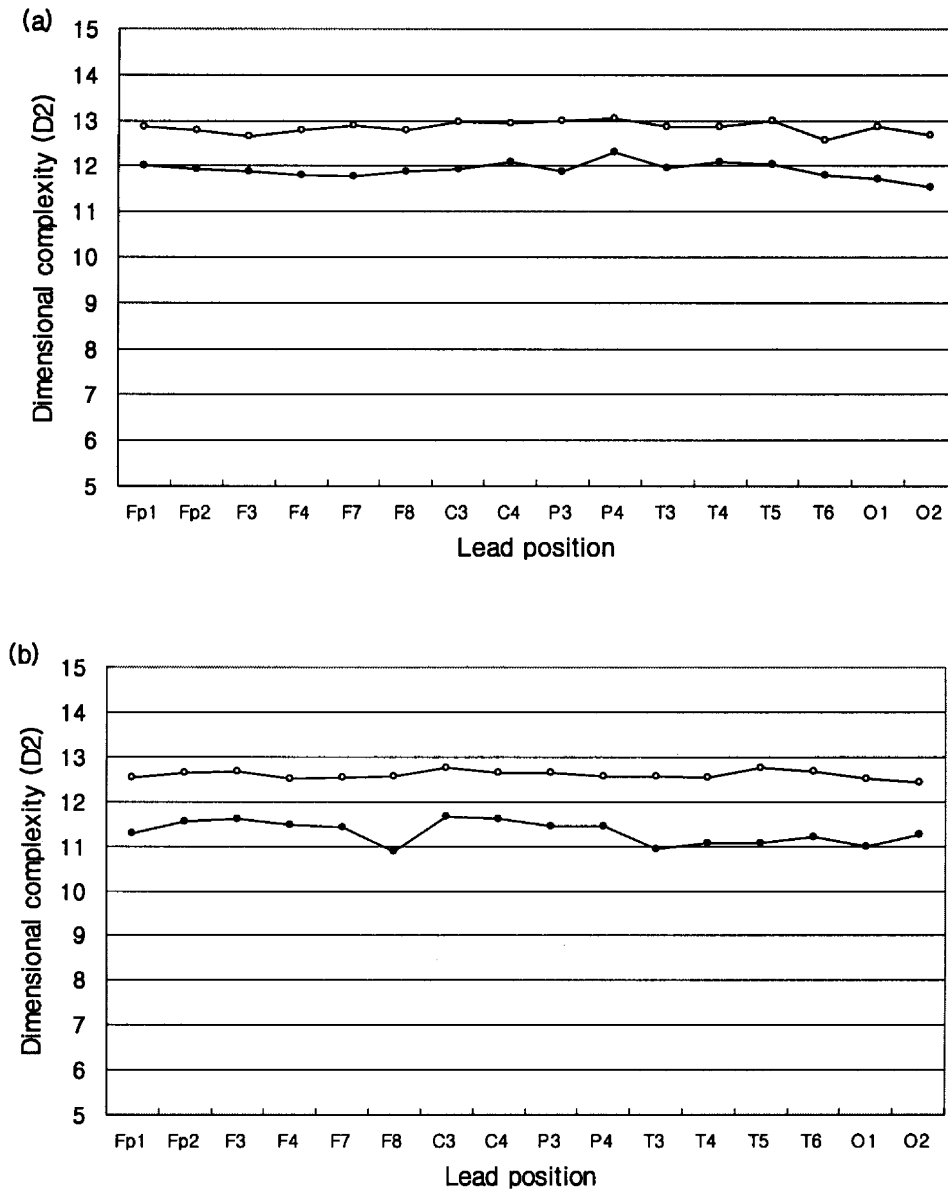


Fig. 1. Mean D_2 values derived from the (●) raw and (○) surrogate EEG data for (a) control and (b) PTSD groups.

pared with control subjects. These results are in general agreement with those of previous studies that have detected abnormal information processing in the brains of individuals with PTSD or other anxiety disorders.

Before discussing our results, we should acknowledge the limitations of this study, includ-

ing a relatively small sample size, the absence of detailed psychometric data, and the inclusion of a heterogeneous study population with a wide range of illness severity and traumatic etiologies. In addition, since many drugs are known to induce EEG changes (Nagase et al., 1996), the possible effect of medication should be pointed out. In this

Table 2

The average D_2 values of the EEG in PTSD patients and healthy controls (post hoc Student's unpaired t -test: d.f. = 39)

Leads	PTSD ($N=27$) mean \pm S.D.	Control ($N=14$) mean \pm S.D.	T	Significance (P)
Fp1	11.30 \pm 0.94	12.01 \pm 0.68	2.49	0.017
Fp2	11.56 \pm 0.86	11.93 \pm 1.12	1.12	NS
F3	11.61 \pm 1.23	11.89 \pm 1.68	1.48	NS
F4	11.48 \pm 0.72	11.81 \pm 0.47	1.54	NS
F7	11.42 \pm 0.54	11.77 \pm 0.69	1.75	NS
F8	10.89 \pm 0.41	11.87 \pm 0.71	4.78	<0.001
C3	11.67 \pm 0.57	11.94 \pm 0.56	1.41	NS
C4	11.61 \pm 0.52	12.10 \pm 0.68	2.56	0.014
P3	11.45 \pm 0.75	11.87 \pm 0.88	1.62	NS
P4	11.45 \pm 0.82	12.30 \pm 0.60	3.45	0.001
T3	10.94 \pm 0.45	11.96 \pm 0.76	5.42	<0.001
T4	11.06 \pm 0.38	12.10 \pm 0.83	4.34	0.001
T5	11.06 \pm 0.45	12.05 \pm 0.63	5.81	<0.001
T6	11.21 \pm 0.68	11.81 \pm 0.59	2.82	0.008
O1	11.00 \pm 0.70	11.72 \pm 0.78	2.99	0.005
O2	11.27 \pm 0.62	11.54 \pm 0.51	1.39	NS

NS: not significant.

study, only patients who were unmedicated for 2 weeks prior to recordings were included. However, the drug-free period was too short to eliminate the

residual effect of drugs, because some patients had taken drugs with a long half life such as fluoxetine.

In spite of these limitations, our results suggest that PTSD patients have globally reduced complexity of their resting EEGs. The reduced EEG complexity indicates in principle that the number of dynamical system variables in the neural processes that generate EEG potentials in the patient population is globally reduced. However, in a less strict sense, this result indicates that CNS information processing of PTSD subjects shows less complex dynamics. The reduced D_2 values may be an expression either of the inactivation of previously active neural networks (Röschke and Aldenhoff, 1991) or a loss of dynamical brain responsivity to normal environmental stimuli (Pritchard et al., 1991). We hypothesize that the pre-occupation with traumatic memories, the re-experiencing of traumatic events, and the concomitant hyperarousal and avoidance defenses—those experiences that comprise the core features of PTSD as a diagnostic entity—interfere with the information-processing capabilities of these individuals. These overly rigid and limited experiential modalities may constitute the deficiencies of infor-

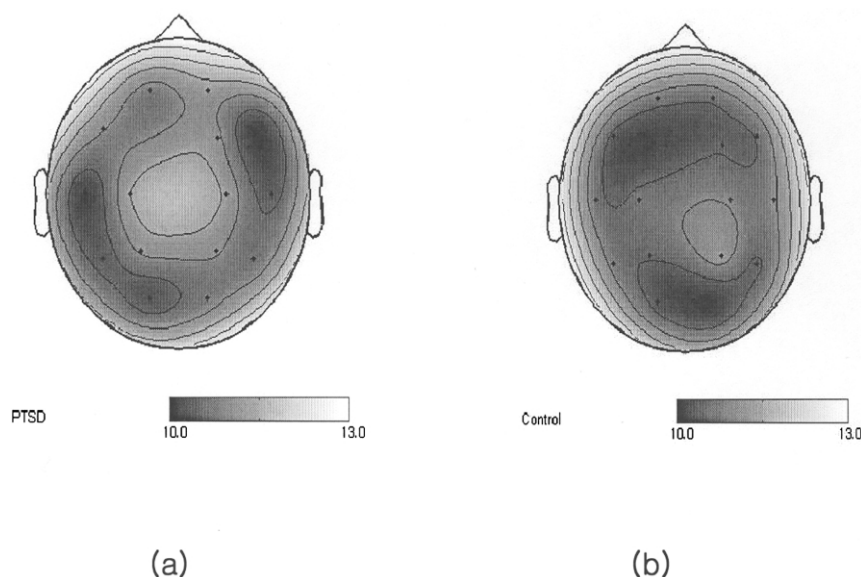


Fig. 2. Graphical distribution of average D_2 values of the EEG in (a) PTSD patients and (b) healthy controls.

mation processing that we detected in these patients. In other words, their information processing and modes of experiencing are more rigid. Consequently, they sustain less complex dynamics of the brain than their healthy control counterparts.

Power spectral analysis of the EEG also demonstrated increased theta activity at the C4 and O1 electrode sites in PTSD patients (Begic et al., 2001). Linear and nonlinear EEG abnormalities in the central region could be related to the change in anatomic structures in PTSD patients, particularly in the amygdala and hippocampus (Charney et al., 1993; Bremner et al., 1995; Gurvits et al., 1996; Bremner et al., 1997). There are some reports which suggest that increased slow waves induce a decrease in complexity of the EEG in schizophrenic patients (Chae et al., 2004) and demented patients (Besthorn et al., 1995, 1997; Jeong et al., 1998b). Several studies have suggested that dysfunction of the amygdala is involved in PTSD symptoms (Shalev and Rogel-Fuchs, 1993). Charney et al. (1993) have suggested that the increased heart rate, skin conductance, blood pressure, and facial electromyographic responses in PTSD reflect alterations in the activity of the amygdala.

Neuroimaging studies have reported increased right prefrontal cortical activity in subjects with anxiety. Increased activity in the right frontal cortex has been associated with a more intense negative affect (Wheeler et al., 1993; Schaffer et al., 1998). The effect of disgust has also been associated with increased right-sided activity in the frontal and anterior temporal regions (Davidson et al., 1990). Emotional withdrawal has been associated with increased right hemisphere activity (Sobotka et al., 1992). Subjects with anxiety, panic disorder, or social phobia show increased activity in right frontal regions when they are anxious (Davidson et al., 2000), and significantly increased blood flow to the right anterior temporal region of subjects with simple phobia has been reported during exposure to phobic objects (Rauch et al., 1995).

Findings from functional imaging studies of PTSD, however, have been more variable and are suggestive of much broader disturbances in neural processing. Increased resting regional blood flow

has been reported in cingulate, limbic, right temporal, and parietal cortices of PTSD patients (Sachinvala et al., 2000). The severity of symptoms in PTSD patients has been reported to correlate inversely with resting blood flow to the caudate nucleus bilaterally (Lucey et al., 1997). Decreased parietal blood flow has been reported in PTSD subjects compared with healthy controls performing an attentional task (Semple et al., 1996). Exposure to stimuli that recall the traumatic event increases blood flow to right limbic, paralimbic, and visual areas (Rauch et al., 1996). Combat sounds increased blood flow to the anterior cingulate, left amygdala, and nucleus accumbens in combat veterans with PTSD (Liberzon et al., 1999), while combat-related pictures increased blood flow to posterior cingulate, precentral, and inferior parietal cortex, and decreased flow to ventral medial prefrontal cortex (Bremner et al., 1999). Recalling and imagining traumatic events in PTSD subjects produced greater increases in blood flow to orbitofrontal cortex and anterior temporal poles than in control subjects (Shin et al., 1999).

These diverse findings suggest that numerous brain regions including frontal, temporal, cingulate and subcortical areas mediate the symptoms of PTSD. Clinical heterogeneity, comorbid psychiatric illnesses, and differences in the anxiety-provoking stimuli used during the scanning sessions may have contributed to the inconsistency of these findings (Osuch et al., 2000). Nevertheless, these imaging findings suggest that broadly distributed brain regions are involved in the pathophysiology of PTSD. This is consistent with the results of the present study that the complexity of the EEG and the underlying neural dynamics that produced it are globally reduced in PTSD subjects.

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