Running head: Abnormal brain waves in PTSD

Imaging the trauma: altered cortical dynamics after repeated traumatic stress

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Abstract

In patients with posttraumatic stress disorder (PTSD), we found evidence of altered systemic cerebral functioning by mapping generators of slow waves produced within circumscribed brain regions. Such focal activities have been associated with lesioned neural circuitry in neurological disorders and more recently also in mental illness. Using magnetoencephalographic (MEG-based) source imaging, we mapped abnormal distributions of generators of slow waves in 97 survivors of organized violence with PTSD in comparison to 97 controls. PTSD patients showed elevated production of focally generated slow waves (1-4Hz), particularly in left temporal brain regions with peak activities in the region of the insular cortex. The left insula has been ascribed a key role in expressing verbal affect, and insular dysfunction could play a key role in the decoupling of emotional from language centers, leading PTSD victims to be caught in the speechless terror of their intrusive memories.

Descriptors

Delta activity, dipole density, magnetoencephalography (MEG), violence, torture, terror,

PTSD

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Repeated traumatic experiences, i.e. highly stressful situations in which the individual is overwhelmed by horror and fear and rendered completely helpless, lead to a high likelihood to consequently develop psychopathology of the trauma spectrum. Prevalence rates of posttraumatic stress disorder (PTSD) between 45% and over 90% have been reported in survivors of torture[1-3]. Left untreated, symptoms may persist for more than four decades[3]. Traumatic experiences induce significant changes in brain function and even structure: in individuals with posttraumatic stress disorder, structural changes have been reported in the hippocampus, amygdala, insula and anterior cingulate cortex[4], and functional changes have been observed in limbic, paralimbic, and prefrontal regions[5-9].

The functional architecture of neuronal networks is reflected in the dynamics of spontaneous neural mass activity, measurable by magnetoencephalography (MEG). The MEG signal arises from magnetic fields produced by intracellular currents. By its nature, MEG measurement filters widespread activity with its radial net currents but is sensitive to circumscribed activity of patches in cortical sulci. An equivalent current dipole (ECD) model provides an excellent approximation to localize such focal assemblies of active pyramidal cells[10].

Abnormally high densities of focal generators of slow waves have been found to be related to brain pathology or dysfunctional neural tissue[11-15]. Brain lesions are frequently accompanied by abnormal slow waves in the deafferented regions, for instance the penumbra after stroke[16] or in circumscribed regions around a tumor[11-14]. Furthermore, it has been shown that focal slow waves are abundant in degenerative disorders such as Alzheimer's disease[17,18] and abnormally distributed in depression and schizophrenia[19-22]. More recently, it has been reported that dissociative experiences in survivors of prolonged torture were reflected in

generators of abnormal slow waves in the left fronto-temporal cortex[23], possibly reflecting the decoupling of frontal affective processors from left perisylvian language areas. These data suggest that abnormally high densities of focal slow wave generators sensitively identify dysfunctional brain regions even when macroscopic structural lesions or functional alterations are not readily detectable by other imaging techniques.

Previous functional neuroimaging studies on PTSD have investigated brain responses in symptom provocation paradigms. The present work investigates alterations in spontaneous brain activity in victims of severe and multiple extreme stressors, including torture. Magnetic source imaging was applied to map local clustering of slow wave generators in the brains of survivors of severe and repeated torture fulfilling DSM-IV criteria of posttraumatic stress disorder. Given the previous observations, we expected more slow waves in frontal and temporal brain regions in PTSD patients compared to controls.

<div align="center">Results</div>

Voxel-based Analysis

Enhanced abnormal slow wave activity was observed in voxels in left temporal areas in the region of the insula in individuals with PTSD compared to controls, whereas in voxels in parieto-occipital areas less slow waves were observed in the PTSD compared to the control group (Figure 1).

Mask-based Analyses

Analysis of z-values. Permutation tests revealed a significant interaction of Group × Region, $p < .001$, whereas Group × Hemisphere failed significance, $p = .10$. Subsequent contrasts showed that PTSD patients exhibited smaller z-values than the control group over parieto-

occipital areas, $p < .001$, $d = .85$, whereas over frontal, central and temporal areas no significant differences between individuals with PTSD and controls were observed.

Analysis of mean z-values above 2 SD threshold (Average above threshold: AvgAbThre). Permutation tests showed an interaction of Group × Hemisphere × Region, $p = .008$. Contrasts revealed larger AvgAbThre values in the PTSD compared to the control group over left temporal, $p = .003$, $d = .43$, and right frontal sites, $p = .03$, $d = .33$ (see Figure 2).

Analysis of maximal z-values in each region (Max). Regions generating pronounced foci of slow waves, i.e. AvgAbThre values, also produced high Max values. Permutation tests revealed an interaction of Group × Hemisphere × Region, $p = .03$. Larger Max values were observed for individuals with PTSD compared to control subjects over left temporal, $p < .001$, $d = .56$, left central, $p = .05$, $d = .30$, left parietooccipital, $p = .03$, $d = .37$, and right frontal sites, $p = .05$, $d = .30$ (see Figure 3).

Discussion

Analyzing the source of focally generated slow waves by means of magnetic source imaging revealed a highly consistent regional pattern in individuals with PTSD compared to healthy controls: PTSD patients showed higher average dipole densities above a threshold of 2 *SD* (AvgAbThre) and higher maximal dipole densities (Max) in left temporal and right frontal areas in comparison to controls. The enhanced presence of slow wave producing foci in the left intrasylvian cortex of PTSD patients compared to controls demonstrates altered functioning, possibly a dysfunction of the left insula in PTSD psychopathology. This corresponds very well with the results of the voxel-wise analysis of dipole densities, which revealed significantly larger dipole densities in PTSD patients compared to controls in the left

insula. Supporting such an interpretation, the right PFC together with the left insula/putamen region has been found to be specifically associated with psychological stress[24], and thus these regions might be particular targets of stress hormones, leading to structural and/or functional damage.

Enhanced left-hemispheric slow wave activity in the intrasylvian cortex

The insula lies deep inside the lateral sulcus in the sylvian fissure under the operculum. It has direct connections with Broca's area[25] as well as with the amygdala and cingulate gyrus[25]. A role of the insula in speech and language processing has long been noted[26], while there is now broad clinical and functional imaging evidence for a participation of the left anterior insula in speech motor control[27]. The left insula is notably larger than the right in most humans[28], consistent with a left-hemispheric dominance in language. Mutism has been frequently observed in cases of insular pathology: Transient mutism is found in cases of left inferior motor cortex damage extending to the insula[29,30], whereas lasting mutism appears to be associated with bilateral lesions of the frontal operculum and anterior insula[31-33]. Functional magnetic resonance studies have revealed significant blood flow increases at the level of intrasylvian cortex during overt speech in the left anterior insula[34,35], suggesting a role of the left insula in the coordination of speech articulation.

Functional neuroimaging studies have also linked insular cortex activation to modulation of affective processing, cognitive and affective processing during learning, and aversive interoceptive processing[36]. Accounting for the role of the insula both in affective and speech processing, the insula has been assumed to influence verbal affect[26]. It has been proposed[27] that the insula might fuse on a moment-to-moment basis linguistic data structures with affective-prosodic information into a smooth motor innervation pattern during speech production.

Recently, the role of the insula in anxiety disorders has received more attention[36]. Indeed, studies investigating volume changes in the brains of individuals with PTSD found evidence for reduced gray matter density in the left insula[4,8]. This insular dysfunction may account for the nonverbal nature of traumatic memory recall in PTSD subjects. Indeed, the hypoperfusion of Broca's area (motor speech) during symptom provocation is a replicated finding[5,6]. Broca's area is necessary for the labeling of emotions, therefore its deactivation under symptom provocation eventually may be due to insular dysfunction in connecting verbal affect with smooth motoric articulation patterns. A disruption of these left fronto-temporal affective language networks would explain why individuals experiencing intrusions and dissociative episodes are unable to actively retrieve and verbalize previous traumatic experiences and why patients with PTSD can experience intense emotions without being able to label and understand them. It is a common experience in clinical practice that patients with PTSD have difficulties in verbalizing their traumatic experiences. The quality of memories during reexperiencing symptoms is more emotional and sensory in nature, whereas feelings cannot be verbally expressed. To put it another way, trauma survivors are caught in speechless terror.

Enhanced right frontal slow wave activity

The enhanced regional slow wave clusters (AvgAbThre) in the right frontal cortex are consistent with the large body of literature on structural, neurochemical, and functional abnormalities in medial PFC, including ACC and medial frontal gyrus, in PTSD[37]. The right PFC has been associated with negative affect, behavioral inhibition and vigilant attention, whereas left-sided PFC regions are particularly involved in approach-related, appetitive goals[38].

The most prevalent functional neuroimaging finding is that of a relatively diminished responsivity in medial PFC (decreased activation and/or failure to activate) in PTSD[37], which would be consistent with the present results indicating PFC dysfunction as indicated by enhanced abnormal slow waves in right frontal areas. Current models on the neurocircuitry of PTSD assume the medial PFC, which plays an important role in fear extinction, to be hyporesponsive, leading to diminished extinction of conditioned fear and together with a hyperresponsive amygdala to augmented fear responses and hyperarousal symptoms[37].

Parieto-occipital slow wave activity

The meaning of differences in parieto-occipital delta dipole densities in PTSD subjects compared to controls in the resting state deserves further investigation. Of particular interest is the present finding of lower levels (z values) but higher left-hemispheric peak (Max) values and a general trend towards more abnormal slow waves over parieto-occipital areas (compare Figures 2 and 3) in PTSD patients compared to controls. This clearly points to the existence of slow wave foci that do not appear in averaged values but differentiate between severely traumatized and non-traumatized individuals. However, currently the functional significance of these findings remains unclear and should be further investigated in future studies.

Conclusions

Extreme traumatic stress such as torture may initially prompt active or passive avoidance strategies in an attempt to reduce overwhelming fear, which may result in a permanent disruption of left fronto-temporal networks. The present results support a functional disconnection of affective from language processing areas as a consequence of trauma-induced plastic changes in torture victims, with a central role of the insula in this decoupling

of brain's emotion and language centers. Furthermore, a dysfunctional PFC may lead to diminished extinction of conditioned fear and reduced inhibition of the amygdala.

Methods

Subjects

194 subjects participated in the study: 97 controls (mean age 30.6 years, *SD* = 10.3, age range 22-66; 56 male, 41 female) and 97 patients (mean age 31.9 years, *SD* = 7.9, age range 16-53; 64 male, 33 female) diagnosed with PTSD according to DSM-IV[39]. All persons were right-handed as measured by the Edinburgh handedness questionnaire[40].

Participants with posttraumatic stress disorder (PTSD) were refugees who came for treatment or expert opinion to the Psychotrauma Research and Outpatient Clinic for Refugees, located at the Center for Psychiatry, Reichenau, Germany. Refugees had the following ethnicities: 74 Turks (71 Kurds), 6 Albanians, 3 Algerians, 3 Romanies, 1 Amharic (Ethiopian), 1 Bosnian, 1 Cameroonian, 1 Georgian, 1 Iranian, 1 Liberian, 1 Serb, 1 Sierra Leonian, and 1 Tamil, and 2 Germans who had fled from prisons of the former German Democratic Republic. In clinical interviews with trained translators, trained psychologists completed the Posttraumatic Stress Diagnostic Scale (PDS)[41], the Hopkins Symptoms Checklist-25 (HSCL-25)[42], or the interviewer-rated 21-item version of the original Hamilton Depression Scale (HAMD)[43]. See Table 1 for mean questionnaire scores and standard deviations. For 40 patients HAMD scores were available as a measure of depressive symptoms, for 57 patients HSCL-scores were available.

Controls were recruited by public newspaper announcements and on campus bulletin boards. All participants provided informed consent and the procedures were approved by the ethics committee of the University of Konstanz. Controls were paid 5 € per hour for participation.

Assessment and Analysis of MEG

The magnetoencephalogram (MEG) was measured in supine position with a 148-channel whole-head neuromagnetometer (MAGNES^{TM} 2500 WH, 4D Neuroimaging, San Diego, USA) during a 5 min resting period. Subjects were instructed to relax but stay awake and fixate a mark on the ceiling of the room throughout the recording period, in order to avoid eye and head movements. A video camera monitored subjects' behavior and assured compliance at any time throughout the experiment. In order to define a subject-related headframe coordinate system and head shapes of subjects, five index points were digitized with a Polhemus 3Space® Fasttrack prior to each measurement. The subject's head position relative to the pickup coils of the sensor was estimated before and after each measurement.

MEG was recorded with a sampling rate of 678.17 Hz and a band-pass filter of 0.1-200 Hz. The electro-oculogram (EOG) was recorded with 2 electrodes attached to the left and right outer canthus of the right eye and 2 electrodes attached below and above the right eye. In addition, the electrocardiogram (ECG) was monitored with 2 electrodes attached to the right collarbone and the lowest left rib. ECG and EOG data were acquired using Synamps amplifiers (NEUROSCAN®). Data were visually inspected for eye blink and eye movement artifacts. While magnetocardiogram (MCG) artifacts were corrected by using the *cardiac remover* (data analysis software WHS version 1.2.5; 4D Neuroimaging), time segments contaminated by EOG artifacts were excluded from further analysis.

Data Reduction and Analysis

Data acquired during the 5 min resting period were reduced by a factor of 16 (antialias filters were applied automatically in the same processing step). Data were digitally filtered in the delta (1.5-4.0 Hz) and theta (4.0-8.0 Hz) band. In each one of five standard channel groups (as defined by 4D Neuroimaging), a single equivalent current dipole (ECD) was fitted for

each time point in the selected artifact free segments to minimize the residual variance. Dipoles were assigned to $2 \times 2 \times 2$ cm³ voxels. Fitted dipoles had to satisfy the following criteria: a) goodness of fit (GoF) > 90%, b) source intensity of 10-100nAm around a focal point source (equivalent to 0.1-1 cm² of activated cortex). Further analysis comprised two different strategies: voxel-based and mask-based.

Voxel-based analysis. Dipole density was estimated for each subject within each voxel of the source volume by calculating the average number of dipoles per time unit in the voxel over artifact free sampling segments. The result is termed „voxel-based dipole density for the i-th voxel" ($VBDD_i$). To obtain a normal distribution across subjects, $LVBDD_i$ was calculated by taking the logarithm of $VBDD_i+1$, which resulted in a value of 0 for empty voxels. For further analysis of individual subjects and visualization, $LVBDD_i$ was z-transformed using the mean and standard deviation of $LVBDD_i$ in the control group. The result is denoted $ZLVBDD_i$.

Using individual head shape information, subjects were aligned to each other. A t-value difference map was calculated comparing $ZLVBDD_i$ values of PTSD patients and controls on a voxel-by-voxel basis. Using AFNI (Analysis of functional neuroimages [http://afni.nimh.nih.gov/afni/about]) the t-value difference map was overlaid with the CH2 brain template (see Figure 1).

Mask-based analysis. Dipole density $VBDD_i$ was averaged over each one of eight regions based on anatomically defined brain masks, generated for temporal, frontal, central and parieto-occipital parts of the brain within each hemisphere following the classification of the anatomical atlas provided with MRICRO's AAL[44]. Empty voxels did not contribute to averages over regions. The result is the mask-based dipole density in region r and hemisphere h ($MBDD_{rh}$). $MBDD_{rh}$ of empty region-hemisphere combinations was set to half the number

of artifact-free epochs of a subject. For further statistical analysis, $MBDD_{rh}$ was logarithmized and *z*-transformed using the mask-based mean and standard deviation in the control group. The result is denoted for simplicity in the following as *z* values.

Max values. Maximal dipole densities within each region-hemisphere combination were calculated by setting Max_{rh} to the maximal value of *z*-values over all voxels i in region r and hemisphere h.

AvgAbThre values. The average dipole density above the threshold of $z = 2$ within region r and hemisphere h was defined as the average dipole density over all voxels in region r and hemisphere h where the density exceeded $z = 2$.

Statistical Analysis

For data analysis, linear mixed effects models[45] were implemented using SAS 9.1 (SAS Institute Inc.). In all analyses of variance (ANOVAs), Subjects served as a random effect nested in Gender and Group[46], whereas all other factors were fixed effects. Differences in dipole density solutions between groups were evaluated by means of a $2 \times 2 \times 4 \times 2$ ANOVA with between factors Group (PTSD patients, controls), Gender (male, female), and repeated measures factors Region (frontal, central, temporal, parieto-occipital) and Hemisphere (left, right).

Because Max and AvgAbthre values cannot be assumed to be normally distributed, ANOVA *F* statistics will not be *F* distributed for these dependent variables. In order to detect significant effects, permutation tests were conducted on the residuals of submodels for each factor and interaction[47,48], holding all other factors and interactions constant by use of restricted permutations. For example, when investigating the significance of Group × Region

× Hemisphere, the vectors of eight residuals corresponding to the eight combinations of Region and Hemisphere were permuted within each subject before being added to the unpermuted values predicted by the submodel defined by excluding Group × Region × Hemisphere from the full model. Next, subjects' group designations were permuted among male and female subjects separately, in order not to include gender effects. The resulting resampled dependent variable datasets were analyzed using the full model. In each case, 1000 permutations were conducted, and the original F value was inserted in the empirical distribution of F values from the resampled ANOVAs. p values as reported below are the difference between 1 and this percentile, such that an original F value falling at the 95th percentile in the resampled F value distribution is considered significant at the .05 level and is reported as $p = .05$. Degrees of freedom are irrelevant in permutation tests and are not reported above. Significant effects were further analyzed by calculating contrasts, applying the same permutation procedure as reported above. For significant contrasts, Cohen's d was calculated as a measure of effect size, using pooled variances[49,50].

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Competing Interests Statement

The authors declare that they have no competing financial interests.

Figure Captions

Figure 1. Axial (left) and coronal (right) view (neurological notation): Depicted are the differences of $ZLVBDD_i$. Only voxels with a significance value of $p < .0004$ are shown. Orange voxels indicate more focal slow waves in the PTSD than in the control group. Blue voxels indicate less focal slow waves in the PTSD than in the control group, with the difference being larger for light blue voxels than for dark blue ones.

Figure 2. Least Square Means of AvgAbhtre (average density above a set threshold – see methods) values for each region in the left and right hemisphere in individuals with PTSD and controls.

Figure 3. Least Square Means of Max values for each region in the left and right hemisphere in individuals with PTSD and controls.

Table 1.

Mean Questionnaire Values (M) and Standard Deviations (SD) of PTSD Patients

Questionnaire	Subscale	PTSD Group		
		N	*M*	*SD*
PDS	Total Score (PDS$_{Sum}$)	97	35.55	7.02
	Intrusions (PDS$_I$)	97	10.71	3.02
	Avoidance (PDS$_A$)	97	13.83	4.04
	Hyperarousal (PDS$_H$)	97	10.86	2.81
HSCL-25	Total Score (HSCL$_{Sum}$)	57	2.97	0.47
	Anxiety (HSCL$_A$)	57	2.97	0.56
	Depression (HSCL$_D$)	57	2.99	0.52
HAMD		40	23.37	7.67

Note. PDS, Posttraumatic Stress Diagnostic Scale; HSCL-25, Hopkins Symptoms Checklist-25; HAMD, Hamilton Depression Scale.
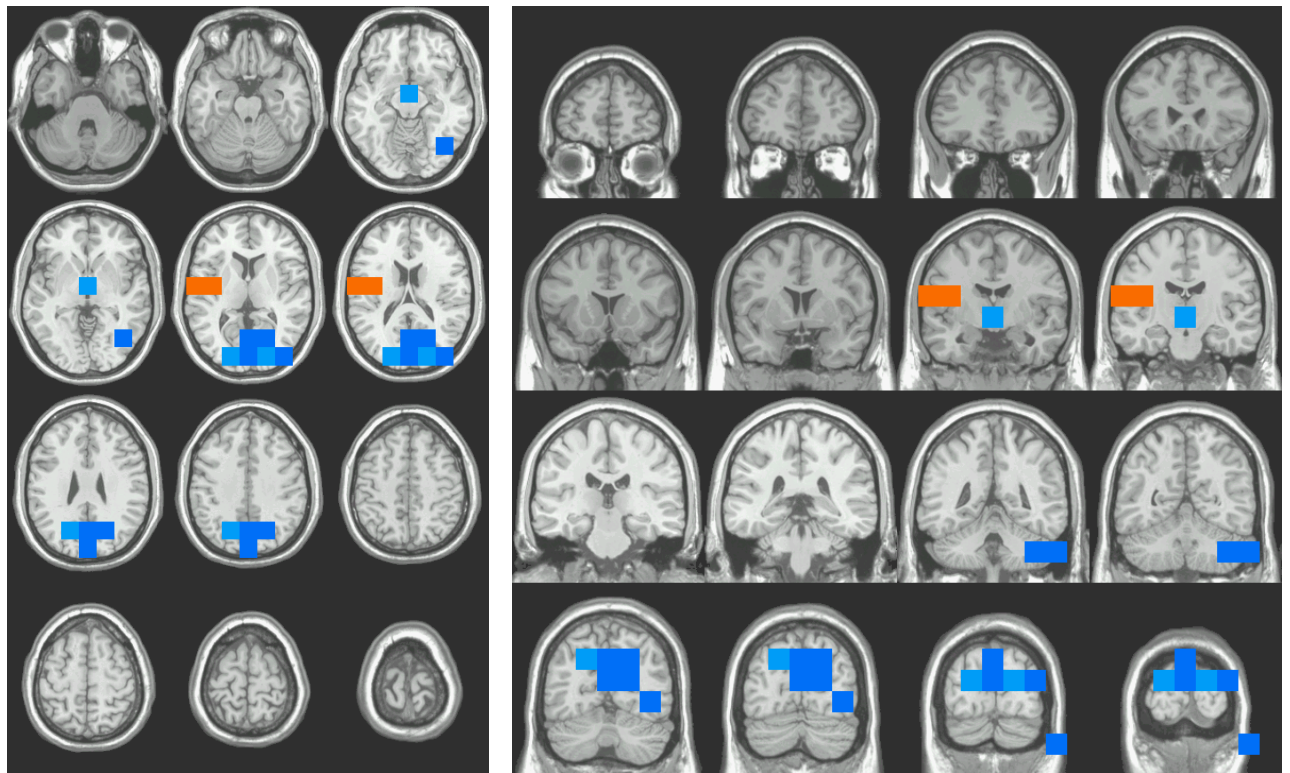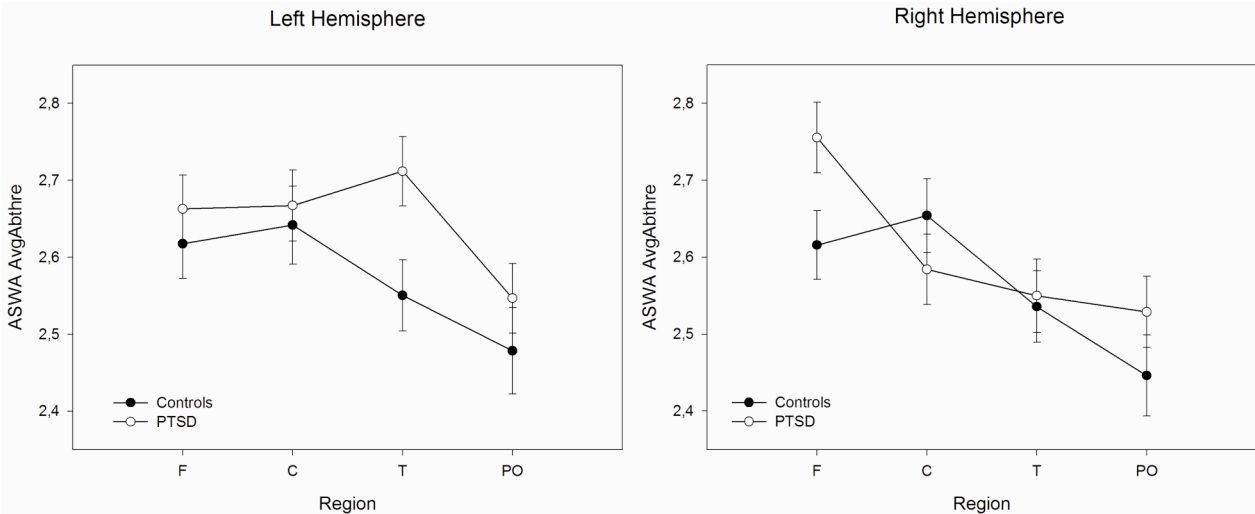
Figure 1

Figure 2

Figure 3