Early Processing of Threat Cues in Posttraumatic Stress Disorder—Evidence for a Cortical Vigilance-Avoidance Reaction

Hannah Adenauer, Steivan Pinösch, Claudia Catani, Hannah Gola, Julian Keil, Johanna Kißler, and Frank Neuner

Background: The present study investigated the influence of posttraumatic stress disorder (PTSD) on early visual processing of affective stimuli in survivors of war and torture.

Methods: Trauma-exposed refugees with ($n = 36$) and without ($n = 21$) PTSD as well as unexposed control subjects ($n = 16$) participated in a magnetoencephalography study with pictures that varied in emotional content.

Results: We found evidence for a biphasic cortical response in patients with PTSD in comparison with the two control groups. In response to aversive (relative to neutral or positive) pictures, PTSD patients showed elevated cortical activity over right prefrontal areas as early as 130–160 msec after stimulus onset followed by a decrease of the affect-related response in the parieto-occipital cortex at 206–256 msec.

Conclusions: The increased early activity in the right prefrontal cortex most likely represents an enhanced alarm response or the fear network toward aversive stimuli in PTSD, whereas the subsequent decreased activation in right parieto-occipital areas in response to aversive pictures seems to reflect the tendency to disengage from emotional content. This finding is consistent with the hypothesis of a vigilance-avoidance reaction pattern to threat in anxiety disorders and helps to reconcile contradicting results of over- and under-responsiveness in the sensory processing of threatening stimuli in PTSD.

Key Words: Attentional bias, neurophysiological correlates, processing of threatening stimuli, PTSD, traumatic stress, vigilance-avoidance

Current theories of posttraumatic stress disorder (PTSD) consider alterations in the processing of threat cues as a core characteristic of PTSD (1). It is assumed that patients with PTSD show a cognitive bias toward unpleasant cues that indicate potential threat (e.g., observing violence or aggressive faces). This bias constitutes the physiological and emotional hyperresponsiveness of PTSD patients (2,3) and is probably a reflection of alterations of basic fear-processing mechanisms. A distinct system (fear network) that enables the rapid detection of threat as well as the immediate initiation of a defensive reaction underlies the neuronal processing of fear. It involves subcortical structures including the amygdala (4,5) as well as cortical regions, in particular the ventral prefrontal cortex (6,7).

Several brain-imaging studies have confirmed that neuronal structures of fear-processing are overly reactive toward threat cues in PTSD. Recent literature reports hyperresponsivity of the amygdala (8) as well as the prefrontal cortex (7) toward aversive stimuli in PTSD subjects. In addition, studies measuring event-related brain potentials (ERPs) consistently found larger attention-related components (P3) after trauma stimuli (9).

Other studies, however, found the opposite effect, (i.e., a reduced cortical reactivity to threat cues in PTSD patients compared with nontraumatized control subjects) (10). Catani *et al.* (11) as well as Weber *et al.* (12), for example, demonstrated that traumatized patients showed a significantly smaller affective modulation of occipital and parietal regions in response to aversive pictures.

One possible explanation for these conflicting findings might be the "vigilant-avoidant" pattern, which has been suggested to account for contradictory results from behavioral and eye-tracking attention studies with anxiety patients (13–15). According to this hypothesis, although aversive cues evoke a rapid response, anxious subjects subsequently initiate attentional avoidance as an attempt to alleviate the fear reaction (13,15). It can be assumed that subjects with PTSD show a strong and immediate processing of aversive cues to allow a rapid detection of threat. This reaction might be essential for survival in a hostile environment with a high risk for retraumatization. Once a stimulus is categorized as threatening, however, further attention allocation toward the stimulus is not necessary and might even be obstructive for the initiation of a flight reaction.

In the present study, we investigated whether both opposing responses can be found in a single experiment: a hypervigilant cortical reaction followed by a subsequent avoidant response. For this purpose, we investigated the time course of the cortical reaction to aversive in comparison with neutral pictures in an event-related field (ERF) study with PTSD subjects. To allow a comparison with the results of recent electrophysiological studies with emotional pictures as stimuli, we adhered to the standard procedure of presenting three categories of images: pleasant, unpleasant, and neutral. In general, these studies found that the early posterior negativity component (EPN) (120–150 msec after stimulus onset) and the late positive potential (LPP) (past 300 msec) are modulated by the emotional quality of a stimulus, which indicates that motivationally relevant stimuli automatically direct attentional resources (16,17).

We expected that PTSD patients would show an increased neuronal excitation after aversive stimulation in the ventral

From the Department of Psychology (HA, SP, HG, JKe, JKi), University of Konstanz, Konstanz, Germany; and the Department of Psychology (CC, FN), Bielefeld University, Bielefeld, Germany.

Address correspondence to Dr. Hannah Adenauer, Department of Psychology, University of Konstanz, 78457 Konstanz, Germany. E-mail: Hannah.Adenauer@uni-konstanz.de.

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prefrontal cortex, which plays a role in stimulus categorization and seems to be reactive to emotional stimuli (6,18). After this early effect, we expected an attenuation of cortical processing in later time windows as a marker of attentional disengagement and cognitive avoidance in sensory processing areas in individuals with PTSD. To disentangle the impact of traumatic exposure and the influence of PTSD, three groups of participants were included in the experiment: PTSD subjects, Trauma Control subjects who reported a history of trauma exposure but did not fulfill PTSD criteria, and Unexposed control subjects. All subjects were refugees, asylum seekers, and immigrants.

Methods

Participants

A total of 73 immigrants from various crisis-affected countries participated in the study. Subjects included asylum seekers and refugees with a history of war and torture who came for treatment or expert opinion to the University of Konstanz Research and Outpatient Clinic for Refugees. In addition, healthy comparison participants with a similar ethnic background were recruited by announcements on campus bulletin boards.

Subjects were divided into three subgroups according to their clinical diagnoses and their traumatic life experiences: 36 participants with a diagnosis of PTSD according to DSM-IV (PTSD group), 21 subjects with a similar background but without current PTSD diagnosis (Trauma Control group), and 16 immigrants with no prior war and torture experiences (Unexposed Control group). Subjects with a current or past history of psychotic disorder or a current alcohol and substance dependence were excluded from the study. The present study is based to a large extent on the sample described in the study by Catani *et al.* (11). Because of the exclusion of a few subjects due to bad magnetoencephalography (MEG) data quality, there are minor differences with respect to sample sizes.

All participants underwent an extensive standardized clinical interview administered by experienced clinical psychologists and trained translators. The number of trauma experiences was assessed by the Life Events Checklist of the Clinician Administered PTSD Scale; Clinical Administered PTSD Scale (CAPS) (19); and the vivo Checklist of War, Detention, and Torture events (20). The CAPS was used for the diagnosis of PTSD and the rating of PTSD symptoms. Furthermore, we assessed diagnoses of comorbid Axis I disorders with the Mini International Neuropsychiatric Interview (MINI) (21). The Hamilton Depression Rating Scale (HDRS) (22) was used to assess severity of depressive symptoms. Descriptive data as well as significant group differences in demographic and clinical variables are presented in Table 1.

Stimuli and Presentation Procedure

A total of 75 colored pictures were chosen from the International Affective Pictures System (23). The pictures were divided according to hedonic valence and emotional arousal: 25 aversive (e.g., mutilations, assaults, weapons), 25 pleasant (e.g., sports, happy couples, children), and 25 neutral pictures (e.g., neutral faces, household objects, landscapes) (specific images are listed in the supplement). These three categories differed significantly in terms of their normative valence ratings (pleasant: 7.4 ± 1.6, neutral: 4.9 ± 1.3, aversive: 2.4 ± 1.5). Although normative arousal ratings did not differ for pleasant and aversive contents, mean arousal levels for both emotional categories were significantly higher than pictures of neutral content (pleasant: 5.6 ± 2.3, neutral: 2.9 ± 1.9), aversive: 5.8 ± 2.3). Color spectra, contrast, and brightness of the pictures were matched across all three categories. Pictures were presented in a pseudorandom order with a video projector (JVC, DLA-G11E) on a gray plastic screen that was attached to the ceiling of the MEG chamber.

Because the design of the study included the analysis of the steady state signal evoked by the emotional stimuli (11), the pictures were presented in a flickering mode of 10 Hz for 4 sec. During the interstimulus interval that varied randomly between 6 and 8 sec, a black fixation cross was presented.

Procedure

Clinical interviews with trauma-exposed participants were carried out 1 week before MEG recording to prevent emotional priming of the reactions to the stimuli by the diagnostic interview. Upon arrival at the laboratory, the participants were provided with a verbal and written explanation of the procedure and gave informed consent to participate. Subjects were seated in a magnetically shielded chamber, and their head shapes were digitized with a Polhemus 3 Space Fasttrack (Polhemus, Colchester, Vermont). Five index points were determined to calculate the relative head position within the MEG helmet for source analysis. After MEG recordings, subjects rated each of the 75 affective pictures regarding emotional valence and arousal with the Self-Assessment Manikin (SAM) self-report scale.

MEG Recording and Preprocessing

The MEG was recorded continuously with a digitization rate of 678.17 Hz with a 148-channel whole head magnetometer (MAGNES 2500 WH, 4D Neuroimage, San Diego, California). A band-pass filter of .1–200 Hz was applied online. For artifact control, electrooculogram and electrocardiogram were recorded with a SynAmps amplifier (Neuroscan) with silver/silver chloride electrodes. Offline, global external noise and cardiac artifacts were corrected by means of procedures included in the MEG acquisition software package (Whole Head system software, version 1.2.5; 4D Neuroimaging). Eye artifacts were corrected with the algorithm implemented in BESA software (24). The MEG data were digitally filtered between 1-Hz high-pass (6 dB/octave) and 25-Hz low-pass (24 dB/octave). After artifact correction, trials containing amplitudes above 3.5 pT (e.g., due to movement artifacts) were discarded from further analysis. The three groups did not differ in the number of accepted trials [Unexposed Group: mean = 73.9, SD = 2.3, Trauma Control subjects: mean = 73.7, SD = 2.2, PTSD: mean = 72.5, SD = 6.7; $F(2,70) = .61$, $p = .55$]. Finally, MEG data were averaged for picture category (pleasant, neutral, and aversive) over 1000 msec (500-msec baseline and 500 msec of stimulus presentation time).

Source Analysis

With the Matlab-based software EMEGS (25), the distribution of the cortical sources of neuromagnetic activity was estimated by calculating L2-minimum-norm solutions that offer enhanced resolution of brain activity generated by a magnetic field without a priori assumption regarding the location and number of current sources (26; Supplement 1). Calculation of the L2-minimum-norm was based on a one-shell spherical head model with 2 (azimuth and polar direction) × 197 evenly distributed dipolar sources. A shell radius of 6 cm was chosen as the best tradeoff