Processing of threat cues: Psychophysiological correlates of posttraumatic stress disorder and changes through psychotherapy

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1 Overview

1.1 Abstract

Posttraumatic stress disorder (PTSD) is characterized by repeated unwanted memories of the traumatic experiences, avoidance of trauma reminders, and general hyperarousal (DSM-IV; American Psychiatric Association, 1994). Symptoms of hyperarousal, especially the excessive reactivity to trauma reminders, indicate a dysfunctional regulation of the physiological stress system in PTSD patients (Buckley & Kaloupek, 2001). Current theories of PTSD consider alterations in the processing of threat cues as a core characteristic of this disorder (A. Ehlers & Clark, 2000). Recent research in PTSD has shown an elevated reactivity to threatening cues across a variety of peripheral physiological measures, including heart rate, blood pressure, skin conductance, and facial electromyograms (Orr & Roth, 2000; Pole, 2007). Neurophysiological studies, however, have yielded inconsistent findings ranging from enhanced (Karl, Malta, & Maercker, 2006) to reduced cortical reactivity to threat cues in PTSD (Weber et al., 2009; Felmingham, Bryant, & Gordon, 2003). Furthermore, it remains unclear whether these physiological alterations can be changed through psychotherapy.

Aim of the present thesis was to investigate psychophysiological correlates of the processing of threat-related stimuli in patients with PTSD. Additionally, we wanted to examine if alterations in the emotional processing could be changed through psychotherapy. The thesis is composed of five journal articles that each constitutes a chapter. In the experiments that are described in the following chapters, we presented IAPS pictures that varied in emotional content, thereby, using a well-established laboratory model of affective processing (P. J. Lang, Bradley, & Cuthbert, 1997, 2005; Junghöfer, Schupp, Stark, & Vaitl, 2005). We applied a steady-state presentation technique, thereby, profiting from a high temporal resolution as well as a good signal-to-noise ratio with a limited number of trials. In addition, this technique allows investigating the time course of cortical activation up to several seconds. During the recordings of physiological data using magnetencephalography (MEG), we presented 75 affective pictures in a flickering mode of 10 hertz for four seconds, respectively.

At first, we developed procedures and routines to analyze the affective modulation of cortical networks with high temporal and spatial resolution. In a sample of 17 healthy participants, the stimulation with affective pictures, compared to neutral pictures, led to enhanced activity in occipital regions. Moreover, we showed that the focus of differentiation was not stable over time, but shifted from occipital into temporal and parietal

regions within the four seconds of picture presentation (see chapter 2).

Afterwards, we carried out the same experiment including 78 individuals with and without PTSD. Study participants belonged to one of the three groups: Trauma-exposed refugees with or without PTSD and healthy individuals with a similar cultural background but without traumatic experiences. We analyzed three different psychophysiological parameters of affective picture processing: Heart rate reactivity, very early cortical activity in the range of milliseconds, and the sustained cortical activity up to four seconds after stimulus onset.

Analyses of the heart rate reactivity revealed differences of the autonomic response between the three groups. Healthy participants showed the typical pattern of initial deceleration in heart rate to aversive stimuli ('orienting response'). PTSD patients, in contrast, reacted with an immediate increase in heart rate towards aversive pictures and an absence of the orienting response. Trauma-exposed participants without PTSD showed an indiscriminate orienting response towards all picture categories (aversive, neutral, and pleasant). Our findings argue for a faster 'flight/fight' response to threatening cues in PTSD. Immediately after having identified the threatening quality of a stimulus, PTSD patients seem to mobilize for action rather than exploring the stimulus further in a vigilant state. In contrast, trauma-exposed controls seem to exhibit a state of permanent alertness towards a wide range of stimuli. It can be speculated that these individuals control their symptoms by permanently scanning the environment for threatening content and by inhibiting the activation of overt reaction (see chapter 3).

Examination of the first 300 milliseconds of neuronal activity during the processing of affective pictures revealed also differences between the three groups. In patients with PTSD, we found evidence for a biphasic cortical reaction pattern. In response to aversive pictures, compared to neutral or pleasant pictures, PTSD patients showed elevated activity over right prefrontal brain areas as early as 130 milliseconds after stimulus onset. This initial increased cortical activity was followed by a decrease of the affect-related response in the parieto-occipital cortex starting 200 milliseconds after stimulus onset. Our results support the idea of a very early 'alarm' response towards aversive stimuli in PTSD, which precedes an attentional disengagement. Thereby, our findings are consistent with the hypothesis of a vigilance-avoidance reaction pattern to threat in anxiety disorders (Mogg, Bradley, Miles, & Dixon, 2004). Moreover, they help to reconcile contradicting results of over- and under-responsiveness in the sensory processing of threatening stimuli in PTSD patients (see chapter 4).

To examine if the attentional disengagement lasts over time, we analyzed the sustained cortical activity over the entire four seconds of picture presentation. Statistical permutation analyses revealed reduced cortical activity over occipital areas in response to aversive pictures in both PTSD patients and trauma controls in comparison to unexposed subjects. Our results indicate that the attentional disengagement from threatening cues lasts up to four seconds. In line with findings of heart rate reactivity, subjects with PTSD seem to focus on the initiation of a rapid flight reaction rather than con-

centrating on the attentive evaluation of the threat cue when confronted with potential threats (see chapter 5).

Main interest of the study was to examine whether these neuropathological alterations in the emotional processing of aversive stimuli could be changed through psychotherapy. In a randomized controlled treatment trial, 34 PTSD patients were randomly assigned to either a group that was treated with Narrative Exposure Therapy (NET) or a waiting-list group. Prior to and four months after the therapy, clinical variables and cortical responses were measured and compared between the two groups. We found a significant reduction in PTSD and depressive symptoms in treated patients. Moreover, parietal and occipital activity to threatening pictures, compared to neutral pictures, significantly increased after therapy in the NET group only. Given the relevance of the parietal cortex in episodic memory retrieval, the enhanced parietal activity after therapy might be linked to a voluntary top-down episodic memory search that is trained by NET. Our results indicate that NET causes a re-establishment of cortical top-down regulation of attention towards aversive pictures. The increase of attention allocation to potential threat cues in patients treated with NET might allow exploring and re-appraising the actual danger of the current situation, thereby, reducing PTSD symptoms (see chapter 6).

Conclusively, this thesis demonstrates that PTSD is characterized by a very specific pattern of physiological responses towards threatening stimuli that can be changed through psychotherapy:

- PTSD patients react with an immediate increase in autonomic activation indicating their readiness for a rapid flight/fight response.
- The cortical processing of threat cues in PTSD is characterized by a biphasic vigilance-avoidance pattern. A rapid increase in cortical activity in prefrontal areas indicates an early alarm or categorization response towards threat. This is followed by a reduced sensory processing of aversive stimuli that lasts up to several seconds after stimulus presentation and might represent a mechanism of attentional disengangement from potential threat.
- These alterations in the cortical processing can be changed through Narrative Exposure Therapy. After therapy, NET patients are able to reduce cognitive avoidance and increase attention allocation towards threatening pictures. Together with a successful memory search, the increase of attention allows treated patients to evaluate the current situation on the basis of previous experiences. This might be linked to a reduction of PTSD symptoms such as chronic hyperarousal and uncontrollable intrusive memories.

1.2 Zusammenfassung

Die Posttraumatische Belastungsstörung (PTBS) ist gekennzeichnet durch sich wiederholende, ungewollte Erinnerungen an traumatische Erlebnisse, eine Vermeidung von Erinnerungsreizen sowie eine generelle Übererregbarkeit (DSM-IV; American Psychiatric Association, 1994). Aktuellen Theorien zufolge stellt die Veränderung in der Verarbeitung aversiver oder trauma-assoziierter Reize ein Hauptmerkmal der PTSD dar (A. Ehlers & Clark, 2000). Eine Reihe von Studien mit PTBS-Patienten, die physiologische Korrelate der aversiven Reizverarbeitung untersuchte, fand eine gesteigerte Aktivität in verschiedenen Parametern wie Herzfrequenz, Blutdruck, Hautleitfähigkeit und Gesichtselektromyogramm (Orr & Roth, 2000; Pole, 2007). Demgegenüber lieferten Studien, die hirnphysiologische Korrelate der PTBS untersuchten, bislang inkonsistente Befunde über erhöhte als auch reduzierte kortikale Aktivität bei der Verarbeitung von Bedrohungsreizen (Karl et al., 2006; Weber et al., 2009; Felmingham et al., 2003). Darüber hinaus ist unklar, ob die genannten physiologischen Abweichungen durch Psychotherapie veränderbar sind.

Ziel der vorliegenden Arbeit ist die Untersuchung psychophysiologischer Korrelate der Verarbeitung von Bedrohungsreizen bei PTBS. Darüber hinaus soll untersucht werden, ob sich diese Abweichungen durch Psychotherapie verändern lassen. Die Arbeit setzt sich aus insgesamt fünf Artikeln zusammen, wobei jeder Artikel jeweils einem Kapitel der vorliegenden Arbeit entspricht. Allen Experimenten, die in den nachfolgenden Kapiteln beschrieben werden, liegt dasselbe Untersuchungsdesign zugrunde: Als Stimulusmaterial zur Untersuchung affektiver Reizverarbeitung dienten Bilder variierender Valenz (P. J. Lang et al., 1997, 2005; Junghöfer et al., 2005). Die kortikale Aktivität wurde mit Magnetenzephalographie (MEG) aufgezeichnet. Wir verwendeten eine steady-state Präsentationstechnik, bei dem 75 IAPS-Bilder in einer Frequenz von 10 Hertz für jeweils 4 Sekunden präsentiert wurden. Diese Technik erlaubt neben einer hohen zeitlichen Auflösung und einem guten Signal-Rausch-Verhältnis die Untersuchung der kortikalen Aktivität über mehrere Sekunden.

Zuerst wurde eine Stichprobe von 17 gesunden Probanden untersucht, um Auswerteroutinen zur zeitlich und räumlich hoch auflösenden Analyse der affektiven Modulation kortikaler Netzwerke zu entwickeln. Dabei zeigte sich eine erhöhte Aktivität in okzipitalen Hirnregionen bei der Stimulation mit affektiven im Vergleich zu neutralen Bildern. Darüber hinaus konnte gezeigt werden, dass der Fokus der Aktivierung über die Messzeit nicht stabil blieb, sondern während der vier Sekunden der Bildpräsentation von okzipitalen in temporale und parietale Hirnregionen wanderte (siehe Kapitel 2).

Das oben beschriebene Paradigma wurde anschließend in einem Experiment mit 78 Personen mit und ohne PTBS-Diagnose angewendet. Die Studienteilnehmer gehören zu einer der drei Gruppen: Traumaüberlebende mit und ohne PTBS, oder gesunde Kontrollprobanden mit gleichem ethnischen Hintergrund, aber ohne traumatische Lebensereignisse. Drei verschiedene psychophysiologische Parameter wurden erhoben: Herzfre-

quenz, frühe kortikale Aktivierung im Bereich von Millisekunden und überdauernde kortikale Aktivierung bis zu vier Sekunden nach Stimulusbeginn.

Bei der Auswertung der Herzfrequenz zeigten sich deutliche Unterschiede zwischen den drei Gruppen in der autonomen Reaktion bei der Betrachtung affektiver Bilder. Die gesunden Kontrollen reagierten analog dem aus der Literatur bekannten Muster: Sie zeigten während der Präsentation aversiver Stimuli eine initialen Abnahme der Herzfrequenz (Orientierungsreaktion). Im Gegensatz dazu reagierten PTBS-Patienten mit einem unmittelbaren Anstieg der Herzfrequenz und einem Ausbleiben der Orientierungsreaktion gegenüber bedrohlichen Bildern. Teilnehmer mit traumatischen Erlebnissen aber ohne PTBS-Diagnose, zeigten, im Unterschied zu den beiden anderen Gruppen, eine initiale Abnahme der Herzfrequenz oder Orientierungsreaktion gegenüber *allen* Bildkategorien (aversiv, neutral und angenehm). Die Ergebnisse weisen auf eine gesteigerte und schnelle Fluchtbereitschaft von PTBS-Patienten hin. Ohne den potenziell bedrohlichen Stimulus zunächst genau zu explorieren, befindet sich das autonome Nervensystem dieser Patienten innerhalb kürzester Zeit in maximaler Alarmbereitschaft. Dem gegenüber scheinen traumatisierte Personen ohne PTBS gegenüber einer Bandbreite von Reizen mit einer erhöhten Wachsamkeit zu reagieren. Möglicherweise entspricht dieses initiale 'Innehalten' und 'Bewerten' der Situation einem adaptiven Mechanismus, der vor der Entwicklung einer PTBS schützt (siehe Kapitel 3).

Bei der Auswertung der ersten 300 Millisekunden neuronaler Aktivität während der affektiven Bildverarbeitung fanden wir ebenfalls Unterschiede zwischen den drei Gruppen. Im Gegensatz zu den beiden Vergleichsgruppen gab es bei den Patienten mit PTBS Hinweise auf ein zweiphasisches kortikales Reaktionsmuster. PTBS-Patienten zeigten bereits in den ersten 130 Millisekunden während der Präsentation aversiver Bilder, im Vergleich zu neutralen oder angenehmen Bildern, eine erhöhte Aktivierung in rechts präfrontalen Hirnregionen. Dieser Aktivierung folgte in zeitlicher Latenz eine Abnahme der Reaktion in parieto-okzipitalen Arealen. Die Ergebnisse unterstützen die Annahme, dass bei PTBS-Patienten ein früher Detektionsprozess von Bedrohungsreizen stattfindet, der einer Abwendung der Aufmerksamkeit vorausgeht. Insofern sind unsere Ergebnisse vereinbar mit der Hypothese eines Übererregungs-Vermeidungs-Musters gegenüber Bedrohungsreizen bei Angststörungen (Mogg et al., 2004). Sie liefern darüber hinaus einen Erklärungsansatz für die bisher widersprüchlichen Ergebnisse von kortikaler Über- und Unteraktivierung bei der sensorischen Verarbeitung von bedrohlichen Reizen bei PTBS (siehe Kapitel 4).

Um zu untersuchen, ob die frühe Abwendung der Aufmerksamkeit von Bedrohungsreizen, die sich bereits innnerhalb der ersten 200 Millisekunden zeigt, über längere Zeit anhält, analysierten wir zusätzlich die überdauernde kortikale Reaktion auf affektive Reize. Statistische Permutationsanalysen ergaben sowohl bei PTBS-Patienten als auch bei Traumakontrollen eine reduzierte kortikale Aktivierung in okzipitalen Regionen bei der Präsentation aversiver Bilder. Unsere Ergebnisse weisen darauf hin, dass die Vermeidung der gezielten Aufmerksamkeitslenkung auf bedrohliche Reize bis zu vier

Sekunden bestehen bleibt (siehe Kapitel 5).

Als Schwerpunkt der Arbeit wurde der Frage nachgegangen, inwieweit sich die neuropathologischen Abweichungen in der emotionalen Verarbeitung durch Psychotherapie verändern lassen. In einer randomisierten, kontrollierten Therapiestudie wurden 34 Patienten mit PTBS einer Behandlungsgruppe mit Narrativer Expositionstherapie (NET) bzw. einer Wartelisten-Kontrollgruppe zugeteilt. Klinische Variablen als auch kortikale Reaktionsmuster wurden vor und vier Monate nach Abschluss der Therapie verglichen. Dabei fanden wir in der NET-Gruppe eine signifikante Reduktion sowohl in der PTBS- als auch in der depressiven Symptomatik. Darüber hinaus zeigten die therapierten Patienten eine signifikante Zunahme der kortikalen Aktivität gegenüber bedrohlichen Reizen in parietalen und okzipitalen Hirnregionen. In Kenntnis der hohen Relevanz parietaler Strukturen beim episodischen Gedächtnisabruf deutet die verstärkte Aktivierung in diesen Arealen auf eine willentlich gesteuerte Gedächtnissuche hin, die durch NET trainiert wurde. Unsere Ergebnisse geben Hinweise darauf, dass Narrative Expositionstherapie die kortikale 'top-down' Regulierung von Aufmerksamkeitsressourcen gegenüber bedrohlichen Reizen wieder herstellt und einen verbesserten Gedächtnisabruf ermöglicht. Die Hinwendung der Aufmerksamkeit zu potenziell bedrohlichen Reizen verbessert die Fähigkeit der behandelten Patienten, die tatsächliche Gefahr einer aktuellen Situation einzuschätzen und vor dem Hintergrund früherer Erlebnisse zu bewerten (siehe Kapitel 6).

Zusammenfassend zeigt diese Arbeit, dass PTBS durch ein spezifisches physiologisches Reaktionsmuster gegenüber bedrohlichen Reizen gekennzeichnet ist, das sich durch Narrative Expositionstherapie verändern lässt:

- PTBS-Patienten reagieren mit einer unmittelbaren Aktivierung des autonomen Nervensystems, was ihre Bereitschaft für eine rasche Flucht/Kampf Reaktion widerspiegelt.
- Die kortikale Verarbeitung von Bedrohungsreizen zeichnet sich durch ein zweiphasisches Übererregungs-Vermeidungs-Muster aus. Die schnelle Zunahme der kortikalen Aktivität in präfrontalen Arealen weist auf ein frühes Alarmsystem bei potenzieller Berohung hin. Diese Reaktion ist gefolgt von einer reduzierten sensorischen Verarbeitung, die bis zu einigen Sekunden anhält. Dies stellt vermutlich eine Vermeidung der detaillierten Exploration potenzieller Bedrohung dar.
- Diese Abweichungen in der kortikalen Reaktion bei PTBS-Patienten lassen sich durch Narrative Expositionstherapie (NET) verändern. Nach der Therapie sind NET-Patienten in der Lage, kognitive Vermeidungsmechanismen gegenüber Bedrohungsreizen zu reduzieren und damit eine adäquatere Verarbeitung dieser Reize zu ermöglichen. Die Stärkung der willentlichen Gedächtnissuche durch NET ist notwendig, um die aktuelle Situation vor dem Hintergrund früherer Erlebnisse

zu bewerten. Möglicherweise steht die Veränderung in der neuronalen Verarbeitung trauma-assoziierter Reize im Zusammenhang mit der Reduktion der PTBS-Symptomatik nach der Therapie.

1.3 Submitted articles and research contributions

The articles in this thesis were realized with the support of a number of colleagues. In the following, I list the submitted articles and my independent research contributions.

Article 1: Imaging cortical activity following affective stimulation with a high temporal and spatial resolution
Julian Keil[1], Hannah Adenauer[1], Claudia Catani[2], Frank Neuner[2]
Epub July 17, 2009 in BMC Neuroscience

I carried out a large number of clinical interviews and MEG recordings. I supported the development of the procedures and routines for MEG data analyses and helped to draft the manuscript.

Article 2: Is freezing an adaptive reaction to threat? Evidence from heart rate reactivity to emotional pictures in victims of war and torture
Hannah Adenauer[1], Claudia Catani[2], Julian Keil[1], Hannah Aichinger[1], Frank Neuner[2]
Epub December 16, 2009 in Psychophysiology

I carried out a large number of clinical interviews, the heart rate recordings, the data preprocessing, and the final analyses of the physiological data. I performed the statistical analyses and drafted the manuscript.

Article 3: Early processing of threat cues in posttraumatic stress disorder – evidence for a cortical vigilance-avoidance reaction
Hannah Adenauer[1], Steivan Pinösch[1], Claudia Catani[2], Hannah Aichinger[1], Julian Keil[1], Johanna Kissler[1], Frank Neuner[2]
submitted

I carried out a large number of clinical interviews, the MEG recordings, the data preprocessing and the MEG data analyses. I performed the statistical analyses and drafted the manuscript.

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Article 4: Pattern of cortical activation during processing of aversive stimuli in traumatized survivors of war and torture
Claudia Catani[2], Hannah Adenauer[1], Julian Keil[1], Hannah Aichinger[1], Frank Neuner[2]
Epub April 10, 2009 in European Archives of Psychiatry and Clinical Neuroscience

I carried out a large number of clinical interviews, the MEG recordings, and the data pre-processing. I supported the development of procedures and routines for MEG data analyses.

Article 5: Narrative Exposure Therapy for PTSD increases activity in cortical regions associated with top-down processing of aversive stimuli – evidence from a randomized controlled treatment trial
Hannah Adenauer[1], Claudia Catani[2], Hannah Aichinger[1], Julian Keil[1], Martina Ruf[1], Frank Neuner[2]
submitted

I carried out a large number of the clinical interviews and NET therapies. I carried out the MEG recordings and performed the data pre-processing and the source estimation. I supported the development of procedures and routines for MEG data analyses. I performed the statistical analyses and drafted the manuscript.

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2 Imaging cortical activity following affective stimulation with a high temporal and spatial resolution

2.1 Abstract

Background The affective and motivational relevance of a stimulus has a distinct impact on cortical processing, particularly in sensory areas. However, the spatial and temporal dynamics of this affective modulation of brain activities remains unclear. The purpose of the present study was the development of a paradigm to investigate the affective modulation of cortical networks with a high temporal and spatial resolution. We assessed cortical activity with MEG using a visual steady-state paradigm with affective pictures. A combination of a complex demodulation procedure with a minimum norm estimation was applied to assess the temporal variation of the topography of cortical activity.

Results Statistical permutation analyses of the results of the complex demodulation procedure revealed increased steady-state visual evoked field amplitudes over occipital areas following presentation of affective pictures compared to neutral pictures. This differentiation shifted in the time course from occipital regions to parietal and temporal regions.

Conclusions It can be shown that stimulation with affective pictures leads to an enhanced activity in occipital region as compared to neutral pictures. However, the focus of differentiation is not stable over time but shifts into temporal and parietal regions within four seconds of stimulation. Thus, it can be crucial to carefully choose regions of interests and time intervals when analyzing the affective modulation of cortical activity.

2.2 Background

Research in affective neuroscience supports the notion that emotional cues guide selective visual attention and receive enhanced processing (P. J. Lang et al., 1997; Öhman, Flykt, & Lundqvist, 2000; Vuilleumier, 2005; Derryberry & Tucker, 1991). In a study

using functional magnetic resonance imaging (fMRI), P. J. Lang, Bradley, and Cuthbert (1998b) found that the functional activation in visual areas of the occipital cortex varied as a function of affective arousal. Other fMRI studies revealed increased BOLD (Blood Oxygen Level Dependent) signals in associative visual regions and subcortical limbic structures when viewing emotionally arousing compared to neutral pictures (Junghöfer et al., 2005; Sabatinelli, Bradley, Fitzsimmons, & Lang, 2005). However, as fMRI measures of blood oxygen level dependent responses take several seconds to build up, they are not able to provide information about temporal characteristics of emotional picture processing. Given the low temporal resolution of the BOLD response and its relation to metabolic processes rather than to neuronal functioning, it has been suggested to use measures that complement the information obtained by hemodynamic imaging techniques (A. Keil, Moratti, Stolarova, Bradley, & Lang, 2003) and thus provide additional information on the temporal characteristics of emotional picture processing (A. Keil et al., 2002). While the combination of the measurement of the BOLD-signal in the fMRI and visual evoked potentials (VEP) promises to solve the problem of the low temporal resolution, this combination might not lead to more accurate results, as two different processes could be active, namely the fast transients of the event related potential and the slow change of blood flow.

In accordance with this notion, an early difference in the visual processing of emotional (pleasant and unpleasant) compared to neutral pictures is revealed by the early posterior negativity (EPN) developing around 120–150 ms after stimulus onset and lasting until about 300 ms (Junghöfer, Bradley, Elbert, & Lang, 2001; H. T. Schupp, Junghöfer, Weike, & Hamm, 2003). This temporo-occipital cortical ERP component reflects the selective processing of emotional stimuli. The amplitude of this component is most pronounced for stimuli of high evolutionary significance. Hence, the early differential ERP response may reflect a very early processing advantage of affective stimuli at the initial stages of perceptual processing (H. Schupp, Flaisch, Stockburger, & Junghöfer, 2006). These findings suggest that the visual cortex is differentially activated as a function of emotional arousal. In addition to these findings in very early time domains, ERP studies have consistently demonstrated a sustained late positive potential (LPP) (past 300 ms) in response to emotional stimuli compared to neutral ones (H. T. Schupp et al., 2000). This posterior cortical ERP component reflects the recruitment of selective attentional processes with respect to motivational significant stimuli. A. Keil et al. (2002) showed a differentiating response to emotionally arousing and neutral pictures in late event related components.

In addition to temporal changes in emotional processing, these studies provide information about the spatial dynamics of affective picture processing. A. Keil et al. (2002) found that the emotional processing within the first milliseconds after stimulus onset is not limited to the primary visual cortex. This study also revealed that, with increasing viewing time (up to 900 ms post stimulus), affect modulation extended from inferior-posterior to higher order visual cortical areas such as parietal and occipito-temporal

regions. These spatial changes can be seen as correlates of longer lasting, higher order processing structures.

However, little is known about the time course of activation in response to emotional stimuli after these early and late event related potentials. Also, as some ERP analyses calculate an average over large sensor clusters, the spatial resolution of the aforementioned studies could significantly be improved by examining the source of activation on the dipole level. Looking at source estimations of activation rather than the recorded topography allows identifying the location of the activation of interest with greater accuracy. While analyzing the topography of activation can be very useful in identifying the general components of the ERP, this procedure lacks the ability to distinctly distinguish between cortical regions. Thus, there is a lack of a reliable and accurate analytical framework to comprise both spatial and temporal changes with high accuracy. Using a source-estimation technique on high-resolution time course data unifies both approaches of an accurate identification of cortical activation and detailed examination of modulations of activation over time. In turn, this would allow the analysis of the network associated with processing of emotional information step-by-step over a long time interval. This might shed light onto the temporal sequence of cortical activation involved in this process. This is especially important given recent findings in our own group that the processing of emotional content is disturbed in anxiety disorders, most prominently posttraumatic stress disorder (PTSD) (Catani, Adenauer, Keil, Aichinger, & Neuner, 2009).

The present study examines an approach to analyze the time course of physiological data that is both spatially and temporally accurate as well as easy and fast to compute. One possibility to account for temporal changes is the steady-state design. The steady-state visual evoked potentials (ssVEPs) (or the steady-state visual evoked field, ssVEF in case of neuromagnetic data) represent a continuous brain response elicited by a repetitive visual stimulus presented at a certain frequency (e.g., 10 Hz). As ongoing cortical oscillatory responses, they have the same fundamental frequency as the driving stimulus (Regan, 1989). One major advantage of the ssVEF technique is that the response of interest can be examined at high temporal resolution and signal-to-noise ratio even when the number of trials is limited. Furthermore, ssVEF data can also be used to investigate the time course of activation over longer time periods up to some seconds (Müller, Andersen, & Keil, 2008). Studies using this paradigm have shown that high arousing pictures generate greater ssVEFs or ssVEPs than neutral low arousing pictures mostly in occipital and parietal cortical networks indicating the allocation of attentional resources to stimuli according to their affective significance (A. Keil et al., 2003; Kemp, Gray, Eide, Silberstein, & Nathan, 2002; Moratti, Keil, & Stolarova, 2004).

However, as these studies have examined the difference between the activation either in terms of an average over the whole steady-state stimulation interval or by reporting the time point of maximum difference (Kemp et al., 2002), it is still unclear which epochs in the interval account for the effect found in the average.

In order to shed light on the temporal and spatial relation of cortical activation, we applied a complex demodulation procedure to minimum norm estimations of cortical activation. The complex demodulation waveform creates an envelope around the baseline-to-peak amplitude of the modulating steady-state signal with high temporal accuracy (Müller et al., 2008) and thus allows for accurate analysis of the temporal characteristics of the ongoing oscillations. We used Magnetoencephalography (MEG) to measure steady-state visual evoked fields (ssVEFs) during the four-second interval of presentation of standardized affective pictures. Pleasant, unpleasant and neutral pictures from the International Affective Picture System (IAPS) (P. J. Lang et al., 2005) were chosen as stimulus material to allow for determining valence-related differences in stimulus processing. Minimum norm estimates (MNE) (Hämäläinen & Ilmoniemi, 1994) were used to estimate the cortical sources of emotion-modulated ssVEFs.

We hypothesized that the peak of activity is not fixed and restricted to primary visual areas but rather shifts as higher order attentional processes come into play. In this way, we tried to analyze the time course of visual processing and attention in the time and space domain over the four-second-presentation interval. The sources of the signal contribution are expected to be located in posterior cortical areas, though not spatially fixed to the primary visual cortex. This represents the alterations of visual processing by emotional content and the interaction with higher order visual cortical areas.

2.3 Methods

2.3.1 Subjects

Seventeen right-handed participants (10 female) with mean age (29.9 ± 6.4 years) and with normal or corrected-to-normal visual acuity gave informed consent to participate in the study. Subjects reported no history of photic epilepsy, had not experienced recent critical life events and had no history of psychotherapy or current psychopathology. The participants received €30 for participation. The ethics committee of the University of Konstanz approved the procedures.

2.3.2 Stimuli

Seventy-five colored pictures were chosen on the basis of their normative ratings from the International Affective Picture System (M. Bradley & Lang, 1994). Of these, 25 pictures presented unpleasant events (e.g., mutilations, assaults, etc.), 25 showed pleasant events (e.g., sports, erotic couples, children, etc.) and 25 showed neutral events (e.g., neutral faces, household objects, etc.). The three categories differed significantly from each other in the normative valence ratings (pleasant: 7.4, neutral: 4.9, unpleasant: 2.4).

Normative arousal ratings did not differ for pleasant and unpleasant contents, but mean arousal levels for both emotional categories were significantly higher than for neutral contents (pleasant: 5.6, neutral: 2.9, unpleasant: 5.8). Brightness, contrast and color spectra of the stimuli were matched across picture categories.

Pictures were presented with a video projector (JVC^{TM}, DLA-G11E) with a refresh rate of 100 Hz on a white plastic screen attached to the ceiling of the room. Pictures subtended a visual angle of 10 ° horizontally and 8 ° vertically to either side from the center of the screen. In each trial, one picture was presented in a flickering mode of 10 Hz for four seconds, resulting in 40 on/off cycles (same picture shown and not shown) of 50 milliseconds each. The inter-trial interval varied randomly between 6 to 8 seconds. In the inter-trial interval a grey screen with a fixation cross was presented to aid participants in maintaining gaze on the center of the screen.

2.3.3 Procedure

Upon arriving at the laboratory, participants were familiarized with the MEG chamber and an informed consent form was signed. Handedness was determined using the Edinburgh Inventory (Oldfield, 1971). For artifact control, four electrodes for the electrooculogram (EOG) were attached; two near the left and right outer canthus and two above and below the right eye. Two electrodes attached at the left and right lower forearm recorded the electrocardiogram, which was monitored during the recording. As the aim of the current study was to introduce a rather new method of analyzing the spatial and temporal course of visual evoked brain activation, the presentation of ECG data would have gone beyond the scope of the paper. Results from the ECG recordings and correlations with several psychological and neural markers will be reported in an additional article. Subjects were then seated in a magnetically shielded chamber and their head shapes were digitized with a Polhemus 3 Space Fasttrack (Polhemus, Colchester, VT, USA). Five index points (left and right periauricular points, nasion, pseudo-Cz and pseudo-inion point at the forehead) were determined to calculate the relative head position within the MEG helmet for source analysis. Finally, subjects were placed under the MEG sensors and instructed to avoid eye movement during picture presentation. A video camera monitored subjects' behavior and assured compliance throughout the experiment.

Then, the screen was positioned in front of the subjects and the presentation of 75 flickering (10 Hz) stimuli started. After MEG recordings, subjects rated each of the 75 affective pictures regarding emotional valence and arousal using the Self-Assessment Manikin self-report scale (M. Bradley & Lang, 1994).

2.3.4 MEG recording

Magnetic brain activity was recorded using a 148 channel whole-head system (Magnes^{TM} 2500 WH, 4D Neuroimage, San Diego, USA). Vertical eye movements and blinks were recorded using Ag/AgCl-electrodes attached above and below the right eye (vertical electrooculogram). Lateral eye movements were recorded using two of the aforementioned electrodes at the outer canthi (horizontal electrooculogram). Electrocardiogram was recorded with two of the same electrodes on the left and right lower forearm. The ECG and EOG data were amplified using Synamps (Neuroscan^{TM}) Amplifiers. The MEG, ECG and EOG data was recorded with a sample rate of 678.17 Hz and filtered online with a band pass filter between 0.1 Hz and 200 Hz.

Procedures included in the MEG acquisition software package (Whole Head System software, version 1.2.5; 4D Neuroimaging) corrected global external noise and cardiac artifacts. Eye artifacts were corrected using the algorithm implemented in BESA^{TM} software (Berg & Scherg, 1994). Trials containing large blink or EMG artifacts or maximum amplitudes above 3.5 pT were discarded from further analysis. The MEG data were digitally band pass filtered between 1 Hz and 25 Hz (slopes: 6 and 24 dB/octave, respectively) before averaging for picture category over 5000 ms (500 ms pre-stimulus, 4000 ms stimulus presentation and 500 ms post-stimulus).

2.3.5 Data Analysis

The data analysis was carried out in two steps: First, the mean amplitude of the 10 Hz component was assessed using a moving window approach. Second, the time course of the modulation of the 10 Hz component over the four second interval of picture presentation was estimated using a complex demodulation technique.

2.3.6 Moving Average

For each category average, the 10 Hz Fourier component was derived using a moving window averaging procedure (A. Keil et al., 2003). To avoid contamination of results with the event related early activity, the initial 500 ms of the picture presentation interval were excluded. The resulting 500–4000 ms post stimulus part of each epoch was baseline-corrected using the 500 ms pre-stimulus interval. A 400 ms window containing four cycles of the 10 Hz flickering stimuli was shifted in steps of 100 ms (one cycle) across the epoch, and the magnetic field data within the shifting windows in the time domain were further averaged.

The resulting four cycles per category, subject and MEG channel were submitted to the fast Fourier-transformation (FFT) technique (Bickford, Fleming, & Billinger, 1971). The real and the imaginary parts of the 10 Hz Fourier component were extracted for further analysis.

2.3.7 Minimum Norm Estimation for the Moving Average Data

The real and imaginary parts of the 10 Hz Fourier component per condition resulting from the procedure mentioned above were submitted to minimum norm source estimation and subsequently recombined by taking the square root of the sum of the two squared dipole orientations. Cortical sources were estimated using the L2 minimum norm estimate (MNE), following the approach suggested by Hauk (2004) using EMEGS (Junghöfer & Peyk, 2004). The L2 minimum norm estimate enables enhanced resolution of brain activations generating the magnetic field without a priori assumptions regarding the location and number of current sources (Hämäläinen & Ilmoniemi, 1994). Calculation of the L2 minimum norm was based on a one-shell spherical head model with 2 (azimuth and polar direction) by 197 evenly distributed dipolar sources. This calculation was based on information on the center of a fitted sphere to the digitized head shape and the positions of the MEG sensors relative to the head. A spherical shell (1 shell, 6 cm, 197 dipoles) with evenly distributed dipole locations then served as source space. This shell was chosen as a compromise between depth sensitivity and spatial resolution (Hauk, 2004). The regularization parameter λ was .02 and thus identical across all subjects and conditions. After computing the minimum norm estimation for the real and imaginary parts of the 10 Hz Fourier component, both values were combined by using the square root of the sum of squares of the two Fourier parts as an estimate of absolute power (Moratti, Rubio, Campo, Keil, & Ortiz, 2008).

2.3.8 Minimum Norm Estimation for the Assessment of Time Course

In order to assess the time course of the steady-state activation, a complex demodulation procedure was applied to minimum norm estimation data. Therefore, in a first step, the minimum norm estimation was computed for the four second interval of picture presentation. Here, we applied the same L2 minimum norm technique as mentioned above, with the difference that a minimum norm estimation was computed for every sample point in the raw data (3391 in total). All other parameters were kept equal. In a second step, the time course of the relevant 10 Hz component was extracted using a complex demodulation procedure. The detailed procedure is described below.

2.3.9 Time Course Assessment

The time course of the amplitude of the 10 Hz steady-state component was computed separately for each dipole using the complex demodulation procedure. This procedure allows reliable extraction of the alterations of the amplitude of an ongoing waveform (Bloomfield, 2004; Papp & Ktonas, 1977). The complex demodulation mathematically extracts a modulating signal from a carrier signal by multiplying the raw data with a sine and cosine of the desired frequency and subsequent band pass filtration. The complex demodulation is computed as follows:

$$x_s(t) = MEG(t) \cdot \sin(2\pi f t)$$
$$x_c(t) = MEG(t) \cdot \cos(2\pi f t)$$

These two functions are applied to the averaged MEG raw data ($MEG(t)$). The frequency f in this case represents the driving frequency (in this case 10 Hz). Then, a 2 Hz Butterworth-filter is applied. The amplitude $A(t)$ of the modulating signal is then described using the formula:

$$A(t) = 2 \cdot \sqrt{x_{s,\text{filt}}(t)^2 + x_{c,\text{filt}}(t)^2}$$

Finally, a baseline correction is applied in the same step using the 500 ms pre-stimulus baseline interval.

2.3.10 Statistical Analysis

As a result of the aforementioned procedures, we obtained two different outcomes: First, we received the mean amplitude of the 10 Hz Fourier coefficients for every dipole as a measure for the averaged activation of the steady-state signal. Second, the complex demodulation procedure was used to derive the amplitude of the 10 Hz signal (component) for every sample point within the four second data interval as a measure of the time course of the activation for each of the 197 projected dipoles. The main goal of the statistical analysis of the MNE data was to show differences between the activation towards the different picture categories. For this purpose, we calculated pair-wise comparisons of the source activities for the three conditions. Condition-dependent activity was reflected by the contrast between activation towards affective (pleasant and unpleasant) and neutral pictures. To test for significant differences between the dipole activation of the three picture categories, we computed permutation tests. This procedure is qualified to cope with the high number of comparisons on dipole level without predetermined regions of interests (Karniski, Blair, & Snider, 1994). Although no formal correction for multiple comparisons (Type 1 error) was made, only temporal and spatial regions comprising several sample points or dipoles respectively were interpreted, thus controlling for by-chance differences.

The advantage of the permutation test is that it does not require any a priori assumption about the distribution of the data, as it generates all possible permutations of the data to represent the data distribution. For each pair-wise condition comparison, we determined cut-off values for significant differences of the condition contrast at single dipole location based on 1000 (moving average) and 500 (time course) draws, respectively. For each draw, the individual condition contrast maps were randomly exchanged to generate data for a random condition composition. As we aimed at two-tailed tests, the maximum as well as the minimum of the differences at all dipole locations obtained

from each draw entered the distributions of 1000 (500 respectively) maximum and minimum difference values. The upper and the lower critical values were determined as the 2.5% lowest and highest value in this distribution. Taken together, these two 2.5% tails represent critical limits of the 95% significance level ($p < .05$). In order to assess the time course, this was done successively for each sample point of the four-second ssVEF interval. Difference values with permutation $p < .05$ were plotted onto a standardized brain. In order to accomplish this, the upper and lower critical difference values were subtracted from the original difference (unpleasant vs. neutral and pleasant vs. neutral) values. Thus, values greater than 0 for the upper critical value and less than 0 for the lower critical value represent the regions and epochs containing significant differences. This yielded maps of significant differences for each sample point between the two affective and the neutral conditions representing the main effect for condition under the null hypothesis that no difference between the conditions exists.

Müller et al. (2008) noted that the greatest steady-state evoked potentials are found at occipital scalp sites. The aim of the present study was to evaluate the course of the activation over time. This includes the assumption that the activation elicited by the steady-state stimulus is not spatially fixed.

2.4 Results

As mentioned above, the following results were obtained using a permutation test yielding significant differences above the 95%-level. Unless stated differently, all results relate to this level of significance. Due to this, no differentiation between levels of significance is being made within the plots. With respect to the mean amplitude estimates, the results of the permutation tests were confirmed using repeated measures ANOVA. The results of the time course analysis were confirmed by point wise t-tests. Where appropriate, the degrees of freedom were corrected in all ANOVA analyses using the Greenhouse and Geisser (1959) procedure to account for possible violations of the sphericity assumption. Bonferroni post-hoc comparisons were used to investigate significant interaction effects.

2.4.1 Mean Amplitude

The estimation of the mean amplitude differences between the three affective categories revealed significantly higher amplitudes towards arousing pictures in the occipital lobe. Also, the unpleasant pictures elicited higher activation compared to the pleasant images. As illustrated in figure 1, the repeated measures ANOVA with the factor condition (pleasant, neutral and unpleasant) confirmed these results ($F(2, 32) = 20.02$, $p < .001$, Bonferroni $p < .05$ for all comparisons).

While the pleasant pictures caused a lower activation in the right parieto-temporal cortex compared to the neutral pictures ($t(16) = -2.82$, $p < .01$; see figure 2), activity

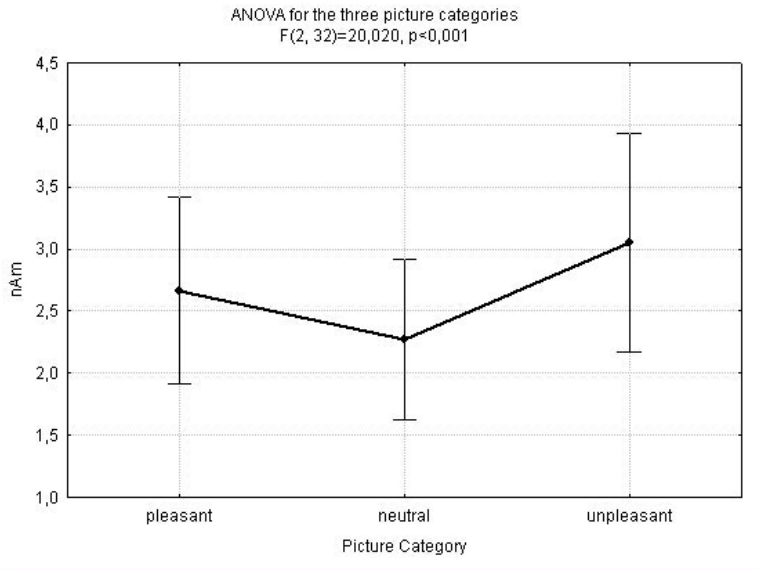

Figure 2.1: Comparison unpleasant vs. neutral vs. pleasant stimuli. Mean condition dependent activation (in nAm) and SE towards high arousing unpleasant, neutral and pleasant slides at the occipital ROI.

in a parietal area was reduced for the unpleasant pictures compared to the pleasant ($t(16) = -1.21$, $p = .23$; see figure 3) as well as the neutral pictures ($t(16) = -1.29$, $p = .2$; see figure 4). The small t-values in these comparisons are due to the large inter-individual variance in these cortical areas.

2.4.2 Time course

The results of the permutation tests identified significant differences between the affective categories and the neutral pictures. Two .mpeg video files illustrate the change of brain activity over the course of the four seconds of picture presentation. These videos exemplify that over time the significant differentiation between the affective categories shifts in space and magnitude[1]. The time course of three regions of interest (occipital, right temporal and parietal) was subsequently analyzed using t-tests to confirm the results obtained by the permutation test. As the results of the comparison of activation towards unpleasant and neutral pictures gave rise to stronger effects, the results of the comparison of pleasant and neutral stimuli will not be discussed explicitly. Significant differences between the unpleasant and the neutral pictures were obtained from the very beginning of the stimulation. As these early components are subject to a tapering procedure in the complex demodulation procedure, the first 500 ms post stimulus

[1] please see for videos online version of this article in BMC Neuroscience 2009, 10:83

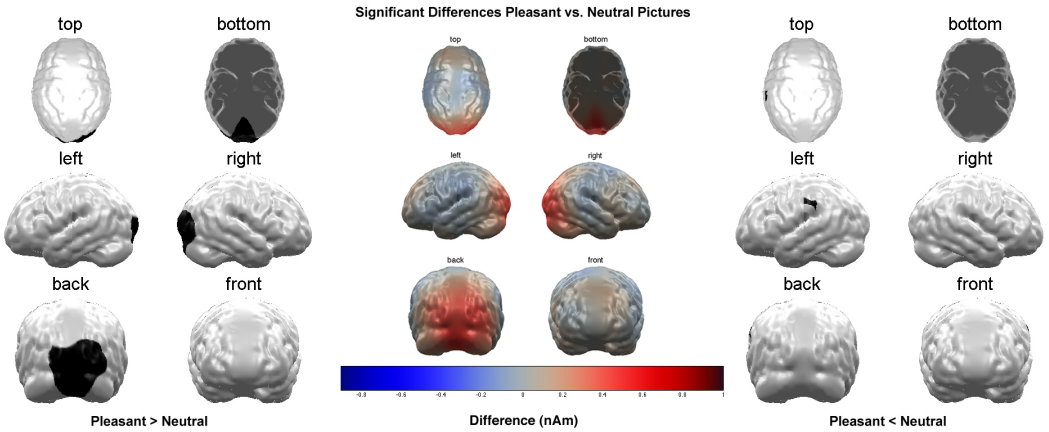

Figure 2.2: Comparison pleasant vs. neutral stimuli. Brain maps showing significant condition differences with respect to cortical source activation towards pleasant and neutral picture content. Depicted are the significant differences in the average over the whole stimulation interval as calculated in the permutation analysis. The left panel shows the areas, where pleasant stimuli lead to higher activation, the right panel shows the areas where neutral stimuli lead to higher activation and the center panel shows the difference of activation that was fed to the permutation analysis.

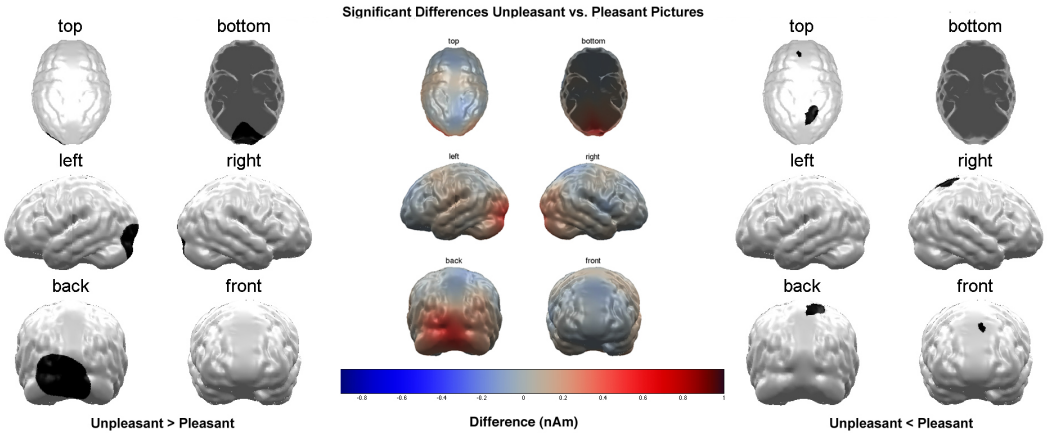

Figure 2.3: Comparison unpleasant vs. pleasant stimuli. Brain maps showing significant condition differences with respect to cortical source activation towards unpleasant and pleasant picture content. Depicted are the significant differences in the average over the whole stimulation interval as calculated in the permutation analysis. The left panel shows the areas, where unpleasant stimuli lead to higher activation, the right panel shows the areas where pleasant stimuli lead to higher activation and the center panel shows the difference of activation that was fed to the permutation analysis.

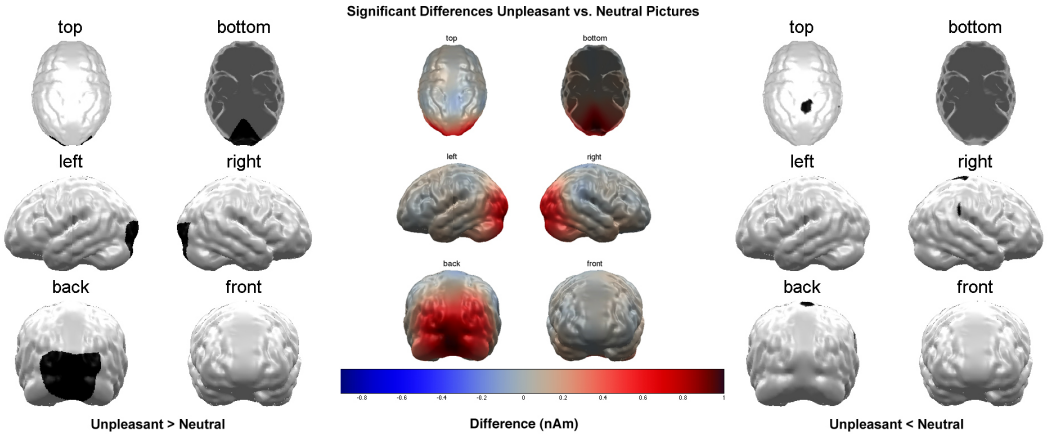

Figure 2.4: Comparison unpleasant vs. neutral stimuli. Brain maps showing significant condition differences with respect to cortical source activation towards unpleasant and neutral picture content. Depicted are the significant differences in the average over the whole stimulation interval as calculated in the permutation analysis. The left panel shows the areas, where unpleasant stimuli lead to higher activation, the right panel shows the areas where neutral stimuli lead to higher activation and the center panel shows the difference of activation that was fed to the permutation analysis.

have to be interpreted with caution and are thus not discussed here. The first differentiation between the affective categories following the initial ERFs was found between 938 ms and 1174 ms post stimulus ($t(16) = 2.79$, $p < .05$). This difference in brain activation within the first second was restricted to the primary visual cortex (see figure 5). The unpleasant pictures elicited higher amplitudes in the primary visual cortex compared to neutral pictures. Over the course of the four second picture presentation, this higher activity regarding affective pictures shifted towards extrastriate cortex in occipito-temporal and posterior parietal cortex areas (see figures 6 and 7). After the initial processing in the primary visual cortex, the differentiation was found between 1140 ms and 1320 ms post stimulus in a temporal region ($t(16) = 2.97$, $p < .01$, see figure 6). This difference between unpleasant and neutral stimuli was found in a parietal region between 2950 ms and 3235 ms post stimulus ($t(16) = 3.83$, $p < .01$, see figure 7).

The pleasant pictures also led to a higher activation in occipital brain regions, although this differentiation was not as pronounced as with the unpleasant pictures. The spatial allocation of activation in the occipital cortical regions was roughly equivalent in response to the pleasant and unpleasant pictures. The initial differentiation was again found in the primary visual cortex and subsequently shifted towards the extrastriate cortex. Pleasant and unpleasant pictures consistently lead to higher amplitudes than neutral images.

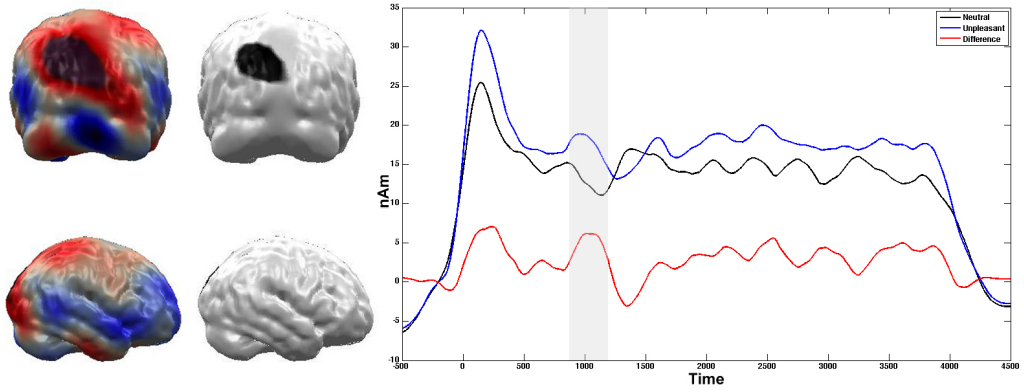

Figure 2.5: Comparison between unpleasant vs. neutral stimuli in the occipital ROI. Time course of condition dependent activation (in nAm) towards high arousing unpleasant and neutral slides at the occipital ROI. Grey areas in the time course plot mark intervals of significant t-comparisons. Brain plots illustrate the ROI (right panel) as well as the mean difference of activation of the marked interval (left panel).

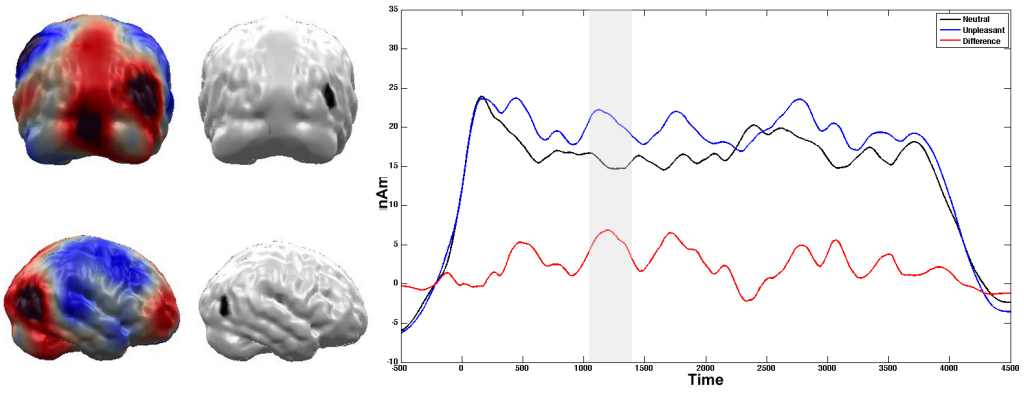

Figure 2.6: Comparison between unpleasant vs. neutral stimuli in the right temporal ROI. Time course of condition dependent activation (in nAm) towards high arousing unpleasant and neutral slides at the right temporal ROI. Grey areas in the time course plot mark intervals of significant t-comparisons. Brain plots illustrate the ROI (right panel) as well as the mean difference of activation of the marked interval (left panel).

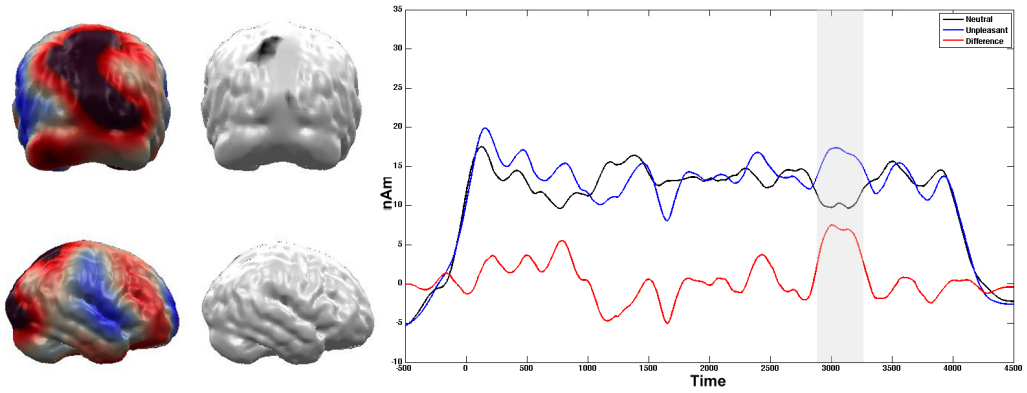

Figure 2.7: Comparison between unpleasant vs. neutral stimuli in the parietal ROI. Time course of condition dependent activation (in nAm) towards high arousing unpleasant and neutral slides at the parietal ROI. Grey areas in the time course plot mark intervals of significant t-comparisons. Brain plots illustrate the ROI (right panel) as well as the mean difference of activation of the marked interval (left panel).

2.5 Discussion

The present study aimed at establishing an accurate and parsimonious paradigm to analyze physiological data over the time course. The paradigm has been applied to the replication and extension of previous findings from studies regarding processing of affective pictures. Consistent with previous research, we found higher activation over occipital areas towards high-arousing pictures in healthy subjects. Both, studies examining ssVEF- as well as ssVEP-changes as a function of emotional arousal have shown greater amplitudes in regions involving the occipital cortices and temporo-parietal cortices (Kemp et al., 2002; Moratti et al., 2004; A. Keil et al., 2003). These findings are typically discussed in the framework of selective attention suggesting that more attentional resources are allocated to external stimuli according to their affective significance to enhance sensory processing of relevant information (P. J. Lang et al., 1997). Hillyard and Anllo-Vento (1998) proposed that attentional processes may be subject to a mechanism of gain control. The authors described a mechanism, which gives input from attended locations an improved signal-to-noise ratio so that more information can be extracted from relevant proportions of the visual field. A. Keil et al. (2003) suggested that the cortical networks for sensory processing might be subject to a gain mechanism according to the motivational relevance as well. That means that not only the attentional relevance but also the motivational relevance (e.g., the fast reaction to potentially threatening stimuli) of a stimulus amplifies the sensory processing of a stim-

ulus. Or to state it differently, motivationally relevant stimuli naturally and perhaps automatically arouse and direct attentional resources (P. J. Lang et al., 1997).

The results of the moving average procedure clearly replicate these aforementioned findings as well as those by Moratti et al. (2004). Emotional stimuli elicit greater ssVEF amplitudes compared to neutral stimuli. The results of the time course evaluation also replicate the findings by Müller et al. (2008) that the greatest differentiation can be recorded at occipital sites.

In addition to these results, we showed that the difference between the activation produced by the affective and neutral pictures fluctuates over time and that the location of the differentiation changes over time. While the results from the moving average procedure point to the primary visual cortex in the occipital region as the area of greatest differentiation between the picture categories, the results of the time course analysis show the additional involvement of extrastriate parietal and temporal brain regions. This is especially important when choosing regions of interest or intervals of interest over which an average is being computed.

With our analysis we could show that affective modulation of cortical activity is not spatially fixed, as can be seen in the different brain maps over the time course. Although the peak of activity can initially be seen in the primary visual cortex within the central occipital region, the location of the peak shifts over time towards secondary and associate visual cortices. This could explain why Müller et al. (2008) could not find a significant difference between the activation following affective and neutral images after 1500 ms post stimulus based on the measurement of a single electrode. Assuming a fixed region of interest for the steady-state data does not allow revealing topographically changing activity that was found by our analysis.

However, the several technical restrictions limit the power of the procedure. As mentioned above, tapers are applied in the complex demodulation procedure. Due to these graduations at the beginning and the end of the resulting waveform, it is not possible to correctly estimate the activity measured in the first and last 500 ms of the stimulus interval. Conventional ERF analysis procedures are better suited to address questions concerning these early potentials, while the complex demodulation procedure is aimed at investigating long-term modulations.

Also, the temporal resolution of the complex demodulation waveform is diffused due to the filtering. Hence, the exact timing of spatial changes in activation is somewhat distorted while the progression of activation is correct. Still, this procedure is able to assess these temporal and spatial changes more accurately than fMRI. While the combination of fMRI and VEP-measurements promise to measure both, fast event-related processing and related hemodynamic changes, it is possible that two different processes occur. When measuring steady-state evoked fields on the contrary, it is possible to examine the spatial and temporal features of cortical information processing with one analytical method.

2.6 Conclusions

Studies using fMRI have identified a variety of cortical areas involved in the processing of emotional information. ERP analyses have suggested a sequential pattern of processing that occur in very brief time periods. Here, we have extended these findings by providing detailed information about the spatial changes over time as well as the temporal characteristics of information processing. Within the first four seconds, the affective modulation of cortical activity is not spatially fixed, but changes locations in occipital, parietal and temporal regions. In this study, we showed that the peaks of affective modulation of cortical activation are unstable already within the first four seconds of stimulus processing. This finding indicates that current models of brain activity based on imaging techniques with a low temporal resolution might be too simplified. The application of a variety of techniques allowing different levels of spatial and temporal resolution is necessary to explore the implications of the temporal variation of cortical activity. The temporal analysis of the ssVEP signal can be one promising tool to obtain more realistic models of brain activity.

2.7 Acknowledgements

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3 Is freezing an adaptive reaction to threat? Evidence from heart rate reactivity to emotional pictures in victims of war and torture

3.1 Abstract

The influence of past traumatic experiences on the defense cascade in response to affective pictures was examined in survivors of war and torture. Trauma-exposed refugees with and without Posttraumatic Stress Disorder (PTSD) as well as healthy individuals viewed 75 pictures that varied in emotional content. Heart rate (HR) was recorded during the flickering stimulation of affective pictures in the context of a steady-state experiment. Whereas healthy controls showed the typical orienting response to aversive stimuli, PTSD patients reacted with an almost immediate increase in HR toward unpleasant pictures. Trauma-exposed participants without PTSD showed an indiscriminate orienting response regardless of picture category. The present findings argue for a faster flight/fight response to threatening cues in PTSD. In contrast, trauma-exposed controls seem to exhibit a state of permanent alertness toward a wide range of stimuli.

3.2 Introduction

The exposure to life-threatening traumatic events can bring about a variety of long-lasting changes in human experience and behavior. Typical consequences interfering with functioning, including repetitive intrusive recollections of the trauma and persistent avoidance of trauma reminders, have been integrated into the diagnosis of posttraumatic stress disorder (PTSD). Physiological symptoms are often the most prominent characteristics of PTSD and include symptoms of chronic hyperarousal. This is apparent in increased irritability and sleeping difficulties. Furthermore, PTSD patients react to reminders of the traumatic event with an increased physiological reactivity. Intrusive recollections of the event are often accompanied by high arousal (Carson et al., 2007; Elbert, Rockstroh, Kolassa, Schauer, & Neuner, 2006).

The chronic hyperarousal and the excessive reactivity to trauma reminders indicate a dysfunctional regulation of the physiological stress system in PTSD patients. Abnormal-

ities in the physiological system have been confirmed in psychophysiological research (Buckley & Kaloupek, 2001). Several studies in PTSD have shown an elevated reactivity to auditory and visual cues associated with the trauma across a variety of physiological measures, including heart rate, blood pressure, skin conductance, and facial electromyograms (Orr & Roth, 2000). Moreover, studies have shown that high resting heart rate in the first days after the traumatic event predicts chronic PTSD (R. A. Bryant, 2006; Shalev et al., 1998).

Some authors have interpreted the elevated physiological reactivity to trauma reminders as an indicator of an excessive stress reaction of trauma survivors. Within the classical stress–response model, the immediate increase of arousal triggered by threat is interpreted as a normal reaction, priming the organism for a rapid fight or flight response. In this context, the enhanced physiological response of the PTSD patients might be interpreted as an adaptive reaction, preparing the trauma survivors for survival in a life-threatening context (Silove, Steel, McGorry, & Mohan, 1998).

However, animal research has shown that an immediate increase of the sympathetic nervous system following a threat cue does not sufficiently account for the defensive reaction of animals (Fanselow, 1994; Timberlake, 1993). Rather, reflex reactivity in defense is organized sequentially, reflecting the proximity or imminence of a threat (M. M. Bradley, Codispoti, Cuthbert, & Lang, 2001). In particular, the fight or flight response is preceded by a short period of freezing behavior, characterized by orienting and information gathering (Bracha, 2004; Gray, 1987). Using finegraded measurement of physiological reactions to emotional pictures, P. J. Lang, Davis, and Oehman (2000) suggested that defensive responding in humans is similarly staged, a phenomenon known as 'defense cascade'. Contrary to the classical stress response model and in line with the defense cascade perspective, several studies have found that the initial reaction to aversive stimuli is characterized by a decrease rather than an increase of heart rate and is accompanied by an inhibition of the startle response (M. M. Bradley, Codispoti, Cuthbert, & Lang, 2001; P. J. Lang et al., 2000). A few seconds after the onset of a threatening stimulus, the direction of the physiological response reverses toward cardiac acceleration and an increase of the startle reflex. The transient pause before the action mobilization is associated with heightened sensory perception and processing of contextual details and has been interpreted as the human counterpart of the freezing state in animals (Graham, 1979; Sokolov, 1963). Therefore, in the present article, we use the term 'freezing' to refer to the very early orienting response toward aversive stimulation. In contrast, 'freezing' in this sense does not refer to the stage 'tonic immobility' (Bracha, 2004) that is associated with later processing stages of threat-related cues.

Although a few studies have applied the concept of orienting response to research in PTSD (Elsesser, Sartory, & Tackenberg, 2004), we have found no study with PTSD patients that analyzed heart rate data following affective stimulation at sufficient temporal resolution to quantify the initial heart rate deceleration in detail. As the decrease of arousal during the orienting response is minimal and transient in comparison to

the following fight/flight state, it is difficult to detect and therefore may have been overlooked in past research. As alterations of the defense cascade are a central feature of PTSD, it is essential to understand these processes in detail. Thus, the aim of the present study was to examine whether repeated traumatic experiences in the context of war and torture are correlated with alterations in the defense cascade, with a particular focus on the orienting response. As heart rate stands out as one of the most reliable correlates of PTSD across all types of psychophysiological PTSD research (Pole, 2007) and as an increase in heart rate is a sensitive marker of PTSD-related reactivity to trauma-related stimuli (Blanchard et al., 1996; M. W. Miller & Litz, 2004), we chose heart rate as the dependent measure for autonomic arousal change. As we aimed at finding evidence for alterations of the defence cascade, we used a standard set of emotional (pleasant, unpleasant, and neutral) pictures that has been shown to trigger defensive reactions before (Blanchard et al., 1996; M. W. Miller & Litz, 2004).

Although the number of traumatic event types is the main predictor for the development of chronic PTSD in war survivors (Neuner, Schauer, Karunakara, et al., 2004), human beings can be astonishingly resilient after traumatic experiences. Many survivors of war and torture do not fulfill the diagnosis of PTSD or recover spontaneously. To account for this, we compared the response pattern of three groups: survivors with a high number of war and torture experiences with a diagnosis of PTSD (PTSD group) and without PTSD (resilient group) and healthy controls with no or almost no past traumatic experience (unexposed group). We expected to replicate the HR response pattern that has often been found in healthy participants. That is, unpleasant pictures prompt the greatest orienting response (indicated by an initial deceleration) followed by pleasant and by neutral pictures, respectively (M. M. Bradley, Codispoti, Cuthbert, & Lang, 2001). In addition, we assumed that PTSD patients would respond with an almost immediate elevation in HR response toward aversive pictures mirroring a high threat state (approaching circa-strike of the predator). Similar results have been obtained with individuals with specific phobia (Hamm, Cuthbert, Globisch, & Vaitl, 1997). For the resilient participants, we hypothesized a response pattern falling in between the two other groups, mirroring a cumulative or dose-response-like relationship of traumatic events and damage to mental health (Neuner, Schauer, Karunakara, et al., 2004).

3.3 Methods

3.3.1 Participants

Fifty-nine war and torture-exposed participants and 19 comparison individuals with no prior war and torture experiences, matched for ethnicity, participated in the study. Trauma-exposed participants were asylum seekers with a history of persecution, war, and torture who came for treatment or expert opinion to the Psychotrauma Research

and Outpatient Clinic for Refugees, located at the Centre for Psychiatry, Reichenau, Germany. This trauma-exposed group was divided according to PTSD diagnosis. Thirty-nine (17 female, 22 male) participants fulfilled DSMIVcriteria for current PTSD (PTSD group) and 20 (13 female, 7 male) survivors of war and torture experiences had not developed PTSD or had already recovered (resilient group). The 19 (11 female, 8 male) comparison participants were recruited by searching for migrants born in conflict regions with hardly any past traumatic experiences by announcements on campus bulletin boards (unexposed group).

PTSD patients were significantly older than the unexposed subjects and less educated when compared to the other two groups. There were no significant differences between unexposed and resilient participants with respect to age and education. Moreover, the three groups differed with respect to asylum status, with fewer PTSD patients having a safe asylum status compared to the other two groups.

All participants underwent an extensive standardized clinical interview administered by experienced psychologists and trained translators. The number of prior trauma experiences was assessed by means of the event checklist of the Clinician Administered PTSD Scale, CAPS (Blake et al., 1995) and the vivo checklist of war, detention, and torture events (Vivo, 2006). Participants in the trauma-exposed group differed in their past experiences of war and torture events, while both groups showed an equally high prior trauma-load of CAPS events.

The CAPS was used for the diagnosis of PTSD and rating of PTSD symptoms (severity and frequency). Naturally, PTSD patients displayed the highest PTSD severity score, and the resilient participants reported more PTSD symptoms than the almost symptomfree unexposed group. Current comorbid DSM-IV axis one disorders were assessed with the MINI International Neuropsychiatric Interviews, M.I.N.I. (Sheehan et al., 1998). The following comorbid diagnoses were present in the PTSD sample: 28 depressive, 4 dysthymic, 2 alcohol abuse, and 1 alcohol dependence disorders. Within the resilient group there were 2 major depressive and 2 dysthymic disorders, and in the unexposed group 1 participant suffered from depressive and 2 participants from dysthymic comorbid disorders. None of the study participants fulfilled the criteria of current or past schizophrenic, paranoid, or other psychotic symptoms.

The Hamilton Rating Scale for Depression, HRSD (J. B. Williams, 1988) was administered to determine the severity of depressive symptoms, and the Screening for Somatoform Symptoms, SOMS-7 (Rief, Hiller, & Heuser, 1997) for the assessment of somatic problems revealed significant differences between the groups in reported depressive as well as psychosomatic symptoms. Equivalent to the PTSD severity, the most somatic and depressive symptoms were reported in the PTSD sample, followed by the resilient participants and the unexposed participants, respectively.

Psychoactive medications taken by the PTSD group were antidepressants ($n = 11$), hypnotics ($n = 7$), neuroleptics ($n = 5$), and anxiolytics ($n = 2$). The resilient group was significantly less medicated: antidepressants ($n = 2$), hypnotics ($n = 1$), and neu-

roleptics ($n = 1$). None of the participants in the unexposed group took psychoactive medication at the time of assessment. Descriptive results as well as significant group differences in demographic and clinical variables are presented in table 1.

3.3.2 Stimuli and Presentation Procedure

Based on normative pleasure and arousal ratings, 25 high-arousing unpleasant (e.g., mutilations, assaults, etc.), 25 pleasant (e.g., sports, children, etc.), and 25 neutral (e.g., neutral faces, household objects, etc.) pictures were chosen from the International Affective Picture System, IAPS (P. J. Lang et al., 2005)[1]. The three categories differed significantly from each other in IAPS normative valence ratings (pleasant: 7.4, neutral: 4.9, unpleasant: 2.4). Arousal ratings did not differ for pleasant and unpleasant contents, but mean arousal levels for both emotional categories were significantly higher than for neutral contents (pleasant: 5.6, neutral: 2.9, unpleasant: 5.8.) Brightness, contrast, and color spectra of the stimuli were matched across picture categories.

As the study included the measurements of the steady-state visual evoked field (not reported here), the pictures were presented for the duration of 4 s in a flickering mode, at a 10 Hz cycle, resulting in 40 on/off cycles. Pictures were shown on a white plastic screen in a pseudorandomorder, with the restriction that no more than three pictures of the same affective category could occur in a row. The interstimulus interval varied randomly between 6 and 8 s.

3.3.3 Heart Rate Recording and Processing

Two Ag/AgCl electrodes positioned on the left and right inner forearms recorded heart rate activity. The usual procedure of taking heart rate recordings from the lower rib cage was considered inappropriately intimate for the multicultural and severely traumatized participants. Heart rate data were amplified with a Synamps (Neuroscan Laboratories, Sterling, VA) and digitized online at a rate of 678.17 Hz.

Heart rate changes following presentation of affective pictures were evaluated using an in-house algorithmwritten in MATLAB (Moratti et al., 2004). The algorithm estimated the heart rate change over 4 s of picture presentation in 250 ms steps using a 1 s prestimulus baseline.

The HR data were scored according to the phasic model of HR change proposed by Hodes, Cook, and Lang (1985). That is, the minimum beats per minute (bpm) value

[1] The numbers of IAPS pictures were as follows: pleasant: 2190, 2214, 2215, 2383, 2440, 2480, 2516, 2840, 2850, 5130, 5510, 5740, 7035, 7175, 7217, 7491, 7500, 7590, 7595, 7700, 8190, 5830, 5660, 4607, 2209; neutral: 1722, 2030, 2058, 2165, 2216, 2311, 2340, 2345, 2352, 4599, 4608, 4641, 4653, 4660, 5260, 5700, 8185, 8200, 8380, 8496, 7490, 7130, 5390, 2570, 2410; unpleasant: 2120, 2900, 3181, 3301, 6190, 6212, 6250, 6312, 6540, 6560, 6831, 6838, 9040, 9181, 9400, 9405, 9415, 9421, 9433, 9911, 6821, 3550, 3530, 2800, 2053.

Table 3.1: Demographic and clinical characteristics of the three groups

		PTSD (n=39)	Resilient (n=20)	Unexposed (n=19)	*p*
Demographic Data					
Sex					0.26
female	*N (%)*	17 (43.6)	13 (65.0)	11 (57.9)	
male	*N (%)*	22 (56.4)	7 (35.0)	8 (42.1)	
Age	*M (SD)*	34.05 (9.15)	29.35 (9.06)	27.32 (9.43)	0.02
Education (ys school)	*M (SD)*	8.26 (3.31)	11.85 (1.87)	12.37 (1.21)	0.001
Regions of Origin					0.06
Middle East	*N (%)*	22 (56.4)	11 (55.0)	6 (31.6)	
The Balkans	*N (%)*	5 (12.8)	5 (25.0)	10 (52.6)	
Africa	*N (%)*	10 (25.6)	4 (20.0)	3 (15.8)	
Caucasus	*N (%)*	2 (5.1)	-	-	
Asylum Status (insecure)	*N (%)*	34 (87.2)	5 (25.0)	1 (5.3)	0.001
Clinical Data					
Events					
Nr Traumatic Events					
CAPS Event-Types	*M (SD)*	6.97 (2.08)	5.65 (1.42)	1.68 (0.89)	0.001
Vivo Checklist					
Nr War&Torture-Types	*M (SD)*	10.74 (5.61)	3.95 (5.56)	0.42 (1.02)	0.001
Raped	*N (%)*	14 (35.9)	2 (10)	-	0.003
Clinical Symptoms					
CAPS	*M (SD)*	79.79 (18.51)	16.25 (21.67)	3.68 (9.01)	0.001
SOMS-7	*M (SD)*	27.05 (12.31)	9.05 (10.54)	3.84 (5.73)	0.001
HRSD	*M (SD)*	25.41 (7.84)	7.45 (7.61)	3.11 (5.8)	0.001
Vulnerability Score					
CAPS Score/Nr War&Tor	*M (SD)*	9.89 (7.14)	4.39 (6.45)	1.00 (1.73)	0.01

Note: For continuous variables ANOVAs were calculated; for dichotomous variables $\chi 2$-tests were applied

during the first 2 s after stimulus onset was scored as the initial deceleration and the maximum value within the next 2 s was considered as the following acceleration.

3.3.4 Procedure

The clinical interviews were carried out 1 week before HR recording in order to control for influences caused by the potential emotional priming by the diagnostic interview. The testing took place in a magnetically shielded chamber because magnetencephalographic (MEG) data were recorded as well (not reported here).

Upon arrival at the laboratory, the participants were providedwith a full verbal and written explanation of the procedures and gave informed consent to participate. After HR recording, participants rated the 75 affective pictures for emotional valence and arousal using the Self-Assessment Manikin (SAM) self-report scale (P. J. Lang et al., 2005).

3.3.5 Statistical Analysis

Demographic and clinical variables were compared using repeated- measures analysis of variance (ANOVA) for continuous variables and the chi-square test for categorical variables. SAM pleasure and arousal ratings were evaluated using repeated-measures ANOVA with group as the between-subjects factor and emotional content (pleasant, neural, and unpleasant) as the within-subjects factor.

Heart rate data were examined for the two different phases (deceleration and acceleration) separately. We applied for each phase a repeated-measures ANOVA with emotional content (pleasant, neural, and unpleasant) as the within-subjects factor and group as the between-subjects factor. Where appropriate, the degrees of freedom were corrected in all ANOVAs using the Greenhouse and Geisser (1959) procedure to account for possible violations of the sphericity assumption. Fisher Least Significant Different (LSD) tests were used to investigate significant interaction effects. A linear regression model was applied to examine potential predictors of heart rate change in aversive picture processing.

3.4 Results

3.4.1 SAM Ratings

As expected, SAM pleasure ratings differed as a function of affective category, $F(2, 114) = 1053.7$, $p < .001$, with pleasant pictures rated as most pleasant followed by neutral pictures and unpleasant pictures rated as least pleasant across all participants. Moreover, analyses of the valence ratings revealed a significant main effect of group,

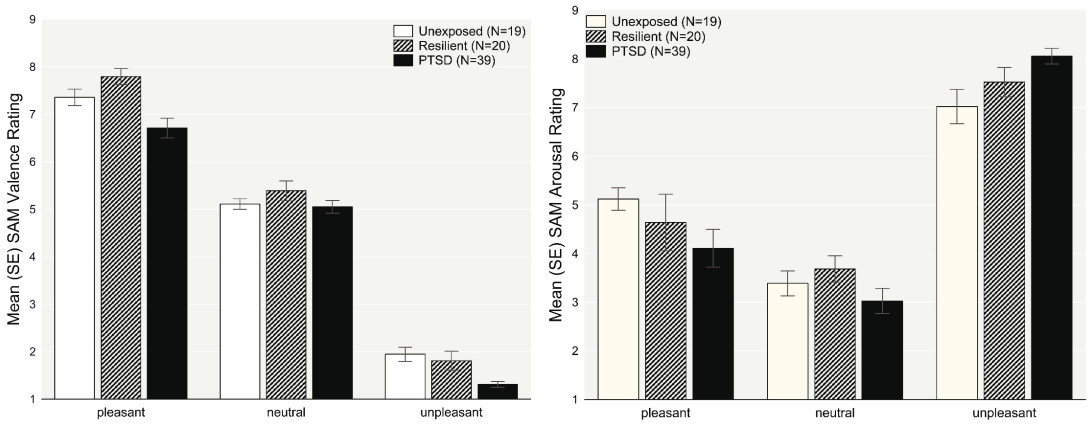

Figure 3.1: SAM valence (left) and SAM arousal (right) ratings of the three groups.

$F(2, 57) = 9.37$, $p < .001$. PTSD patients rated all pictures as less pleasant with respect to the two comparison groups (Fisher LSD $p < .01$ for all comparisons).

Arousal ratings for all participants also varied over affective categories, with unpleasant and pleasant pictures rated as more arousing than neutral pictures, $F(2, 114) = 200.51$, $p < .001$ (Fisher LSD $p < .001$ for all comparisons). Arousal ratings also differed significantly between unpleasant and pleasant pictures (Fisher LSD $p < .001$). Moreover, SAM arousal ratings revealed a significant interaction effect of affective category by group, $F(4, 114) = 5.03$, $p < .001$. There was a trend that PTSD patients rated pleasant pictures as less arousing and unpleasant pictures as more arousing than the unexposed group (Fisher LSD $p > .05$ for both comparisons; Figure 1).

3.4.2 Heart Rate Response

We compared the prestimulus HR of our three groups. There was no significant difference in the averaged prestimulus HR level between the three participant groups, $F(2, 75) = 0.74$, $p > .05$. Regarding the whole stimulation interval of 4 s, every group displayed a very distinct cardiac response pattern toward the three different picture categories. The mean heart rate change relative to prestimulus baseline for each group and for each category (pleasant, neutral, and unpleasant) is depicted in figure 2.

Moreover, the cardiac response of the 4 s of picture presentation showed two distinct phases for all affective categories and all groups as detected by amain effect of phase, $F(1, 75) = 108.62$, $p < .001$. Characteristic of this biphasic model was an initial deceleration and a following acceleration (Fisher LSD $p < .001$).

Within the deceleration phase (in the first 2 s of picture presentation) there was a significant interaction of affective category by group, $F(4, 150) = 3.74$, $p < .01$. This

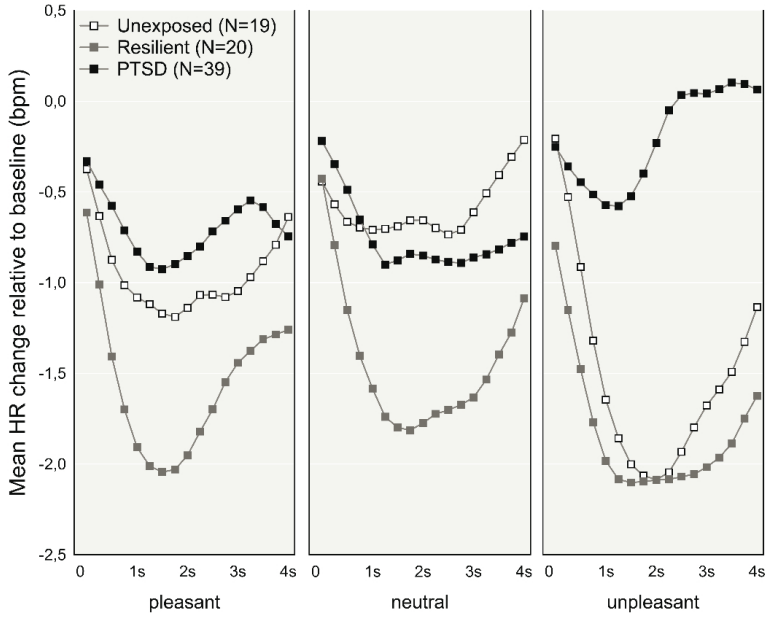

Figure 3.2: The mean heart rate (bpm) changes relative to prestimulus baseline across picture presentation (4 s) for each group and for each category (pleasant, neutral, unpleasant)

difference was characterized by a very weak deceleration toward aversive stimuli in the PTSD group compared to a pronounced deceleration toward the aversive material in the two other groups (Fisher LSD $p < .01$ for the resilient and $p > .05$ for the unexposed group). A main effect of group revealed that the resilient sample showed a stronger initial deceleration, $F(2, 75) = 6.02$, $p < .005$, over all picture categories compared to the PTSD group (Fisher LDS $p < .001$). Intriguingly, these individuals did not display any differences in their HR response patterns between the affective categories (LSD $p > .2$ for all comparisons). Whether pleasant, neutral, or unpleasant pictures were shown, resilient individuals reacted with a pronounced cardiac deceleration. Finally, the unexposed group revealed the expected HR response (M. M. Bradley, Codispoti, Cuthbert, & Lang, 2001) , characterized by an initial deceleration toward all pictures, that was most pronounced for the threatening picture content: main effect of affective category, $F(2, 36) = 4.76$, $p < .01$ (Fisher LSD $p < .001$ for the comparison of neutral vs. unpleasant and $p > .05$ for the comparison pleasant vs. unpleasant). Within the acceleration phase of picture presentation, a significant interaction of affective category and group, $F(4, 150) = 5.22$, $p < .001$, revealed that the effect of a very distinct response pattern of the three groupswas preserved. In the last 2 s of picture presentation a main effect of group, $F(2, 75) = 9.48$, $p < .001$, showed a more pronounced acceleration in the PTSD sample compared to the other two groups (LSD $p < .005$ for both comparisons).

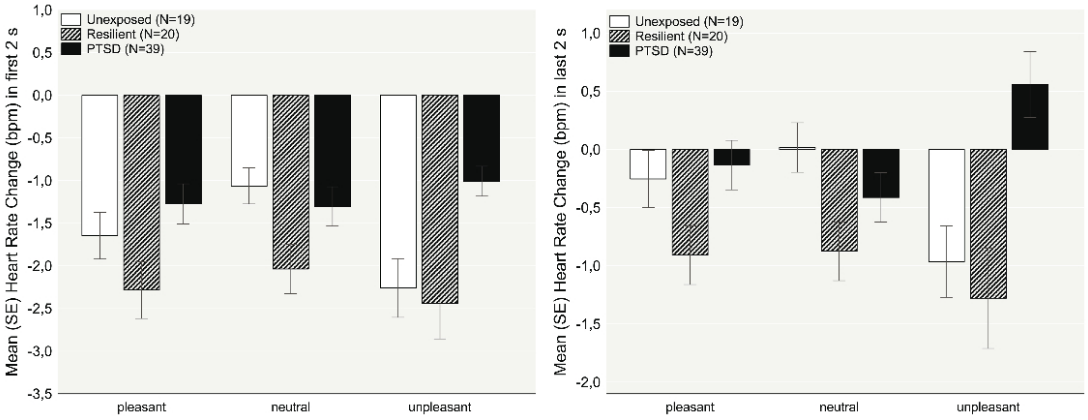

Figure 3.3: The mean heart rate (bpm) changes relative to prestimulus baseline for each group and for each category (pleasant, neutral, unpleasant) for the initial deceleration (left) and the following acceleration (right).

This strong acceleratory response in PTSD individuals was most distinct during the presentation of high arousing aversive images (Fisher LSD $p < .01$ in comparison to pleasant and $p < .001$ compared to neutral pictures). For both phases separately, HR changes relative to a prestimulus baseline for all groups and affective categories are depicted in figure 3.

Given the existing scientific evidence for distinct HR responses toward aversive cues between men and women (M. M. Bradley, Codispoti, Sabatinelli, & Lang, 2001), we calculated an ANOVA with gender as an additional factor both for the initial deceleration as well as the following acceleration of the HR response. Analyses showed that for both time intervals, gender did not have any significant effect. Any interaction yielded statistical significance: initial deceleration, $F(4, 144) = 2.14$, $p > .05$; acceleration, $F(4, 144) = 0.35$, $p > .05$. However, the main effect for group and the interaction between group and category remained significant even if gender was included.

Prediction of initial heart rate changes towards aversive pictures

To examine potential predictors of the heart rate change toward aversive images in the first two seconds after picture presentation, a linear regression model was calculated. Variables that were potentially related to the cardiac response toward aversive visual stimuli were included as the predictor variables. Because our main focus was the orienting response, the initial reaction served as the dependent variable. The 'initial reaction' was defined as the minimum bpm value during the first 2 s after stimulus onset. The unexposed participants were excluded from the analysis because many individuals in this group reported zero or very few PTSD symptoms and few experiences of war and

Table 3.2: Linear regression model with the initial response toward aversive pictures as the dependent Variable.

Predictor	Zero-order correlation	ß
Age	0.30**	0.14
Gender (female)	-0.29*	-0.36**
Vulnerability Factor [a]	0.39**	0.41**
Raped (yes)	-0.18	-0.09
Depression [b]	0.28*	0.02
Immigration Status (safe)	-0.31*	-0.07

Note: Zero-order correlation is represented by Spearman´s rho for continuous predictor variables and point-biseriel correlation for dichotomous predictor variables; ß coefficients are standardized and results from a linear regression model of HR acceleration within the first 2 s of picture presentation; full model adjusted R^2=0.28 for the PTSD and the Resilient group
* p<0.05
** p<0.01
a Vulnerability Factor: CAPS-severity score divided by number of war and torture events
b HAM-D sum score

torture. Results of the analysis are presented in table 2.

The main predictor of the initial HR response toward aversive images was the 'vulnerability factor'. This factor was created by the quotient of posttraumatic symptoms (CAPS sum score) and the number of past war and torture experiences. Accordingly, individuals with a low vulnerability factor were characterized by reporting few symptoms, despite having experienced many war and torture events.

The positive relation between vulnerability and the initial HR response reveals that vulnerable people show a relatively smaller HR deceleration within the first 2 s. Neither age, depressive symptoms, asylum status, nor the experience of rape had a significant influence on the initial heart rate response toward aversive stimuli. Gender resulted as a further significant predictor, with women showing a comparatively stronger deceleration in this time interval.

3.5 Discussion

In agreement with previous research (M. W. Miller & Litz, 2004), we found a cardiac acceleration in response to aversive pictures in patients with PTSD. HR acceleration following aversive stimuli was significantly greater in PTSD patients compared to the

other two groups. Furthermore, in comparison to both the unexposed and the resilient groups, the orienting response to aversive pictures was almost absent in participants with PTSD. This shows that the heart rate response in the face of threat is not only stronger but also faster in those with a diagnosis of PTSD. Our resultsmight indicate that in PTSD the defense cascade had been adjusted to allow for a rapid flight response to threatening cues without any further exploration of the stimulus. This finding is consistent with the observation that PTSD patients react to threatening cues and trauma reminders with a hypersensitive alarm system (Rauch et al., 2000). Furthermore, our findings might have implications for the interpretation of the attentional bias toward threat cues that has been documented in PTSD (R. A. Bryant & Harvey, 1997; Buckley, Blanchard, & Neill, 2000). Our findings suggest that, immediately after having identified the threatening quality of a stimulus, PTSD participants mobilize for action rather than exploring the stimulus further in a hypervigilant state.

Contrary to our assumptions, the resilient group did not show a reaction in between the unexposed group and the PTSD patients but reacted with a specific pattern. In this group, a pronounced indiscriminate orienting response was found for all classes of stimuli including the neutral pictures. These participants who did not develop or who had recovered from PTSD, despite a history of severe past traumatic events, remain in a permanent alert state, which is demonstrated by a distinct orienting behavior toward a wide range of stimuli. However, in contrast to the PTSD participants, who were mobilized and ready for flight, the resilient participants remained in the preencounter stage where the predator has been identified but is still far away. It can be speculated that resilient participants might control their symptoms by permanently scanning the environment for threatening content and by inhibiting the activation of overt reaction.

A cross-sectional design cannot determine the causality of the effects. However, in a tentative analysis, we aimed to explore whether the marked difference between PTSD patients and resilient participants in physiological reactivity to aversive stimuli is constitutional (Guthrie & Bryant, 2005) or acquired (Orr et al., 2003). The regression analysis revealed that vulnerable participants (i.e., individuals with high scores in PTSD symptoms despite relatively few traumatic events) are characterized by an elevated early HR response toward threatening stimuli. Neither depression nor postmigration factors such as the asylum status contributed to the prediction of HR response. Our results give some indication that a pretrauma psychophysiological arousal may represent a vulnerability factor for the development of PTSD, whereas a strong orienting response involving an initial deceleration of HR might represent resilience. However, this hypothesis should be tested in a longitudinal study.

Gender was also a significant predictor for the initial HR response.Yet, because the reanalysis with gender as an additional factor revealed no different outcome, it can be hypothesized that heart rate responses of men and women did not differ substantially. Only if more variables were taken into account did gender receive some predictive value. Results indicate that women show a greater initial heart rate deceleration in response to

viewing aversive pictures compared to men. This finding is in line with previous studies investigating the differences in heart rate responding toward aversive pictures in men and women (M. M. Bradley, Codispoti, Sabatinelli, & Lang, 2001). Badley and collegues (2001) found a stronger deceleration toward aversive pictures in female compared to male subjects and suggested that symbolic picture cues activate the defensive motive system more intensely in women than in men.

What should be noted with respect to the debate about possible gender effects in the present study is that men and women significantly differ with respect to the amount of war and torture they have experienced ($t = 3.24$, $df = 54$, $p < .005$). Men reported significantly more types of war and torture events when compared to their female counterparts. This confounding effect was another reason why we decided not to focus our analyses on group differences between men and women. Future studies should ideally include female and male trauma survivors with a comparable quantity and quality of traumatic experience, thereby allowing researchers to clearly disentangle gender effects from effects related to trauma severity.

A limitation of the present study is that group differences cannot be solely attributed to PTSD status because there were substantial differences between groups in terms of comorbid disorders, including depression. However, this problem is inherent in most PTSD research because PTSD is commonly associated with other disorders. A restriction to participants without comorbid disorders limits the generalization of results to participants with less serious traumatic events whomight present with a qualitatively different picture. In addition, the groups differed with respect to medication. Although there is no indication that differential HR reactivity in general is affected by antidepressant medication, this effect cannot be ruled out as a confounding factor. Further studies should try to find samples without medication or increase sample size to allow a subgroup analysis depending on medication status. Finally, to address the question of whether possible avoidance mechanisms might have contributed to the finding of a weaker orienting response in PTSD, future studies should ideally measure eye movements in addition to the HR response.

Our results suggest that trauma-exposed participants with and without PTSD as well as healthy participants can be discriminated on the basis of their pattern of heart rate reactions to emotional stimuli. Moreover, the findings indicate that dysfunctional as well as functional alterations of the defense cascade can be observed in victims of war and torture. The absence of an orienting response to aversive pictures in PTSD patients and the dominance of the freezing state in resilient participants indicate that an orienting response might be adaptive and prevent a maladaptive physiological arousal or flight response after traumatic exposure.

3.6 Acknowledgements

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4 Early processing of threat cues in posttraumatic stress disorder – evidence for a cortical vigilance-avoidance reaction

4.1 Abstract

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 controls (n = 16) participated in a magnetoencephalography study using pictures that varied in emotional content.

Results We found evidence for a biphasic cortical response in patients with PTSD in comparison to 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 ms after stimulus onset followed by a decrease of the affect-related response in the parieto-occipital cortex at 206–256 ms.

Conclusion The increased early activity in the right prefrontal cortex most likely represents an enhanced orienting response or the fear network towards 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.

4.2 Introduction

Current theories of posttraumatic stress disorder consider alterations in the processing of threat cues as a core characteristic of PTSD (A. Ehlers & Clark, 2000). It is assumed that patients with PTSD show a cognitive bias towards unpleasant cues that indicate potential threat (e.g., observing violence or aggressive faces). This bias constitutes the physiological and emotional hyperresponsiveness of PTSD patients (McNally,

Clancy, Schacter, & Pitman, 2000; Buckley et al., 2000) 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 (B. J. Liddell et al., 2005; LeDoux, 2000), as well as cortical regions, in particular the ventral prefrontal cortex (Kawasaki et al., 2001; R. Bryant et al., 2008).

Several brain-imaging studies have confirmed that neuronal structures of fear processing are overly reactive towards threat cues in PTSD. Recent literature reports hyperresponsivity of the amygdala (Shin, Rauch, & Pitman, 2006) as well as the prefrontal cortex (R. Bryant et al., 2008) towards aversive stimuli in PTSD subjects. In addition, studies measuring event-related brain potentials (ERPs) consistently found larger attention-related components (P3) following trauma stimuli (Karl et al., 2006).

Other studies, however, found the opposite effect, i.e. a reduced cortical reactivity to threat cues in PTSD patients compared to non-traumatized control subjects. Catani, Adenauer, et al. (2009) as well as Weber et al. (2009), for example, demonstrated that traumatized patients showed a significantly smaller affective modulation of occipital and parietal regions in response to aversive pictures as compared to healthy control participants. Moreover, Felmingham et al. (2003) reported a reduced ERP signal in PTSD in response to affective faces.

One possible explanation for these conflicting findings may be a 'vigilant-avoidant' pattern of the cognitive bias in anxiety disorders. According to this hypothesis, whilst aversive cues evoke a rapid and intense initial automatic orienting response, anxious subjects initiate attentional avoidance to the stimuli as a attempt to alleviate the fear reaction (Koster, Verschuere, Crombez, & Van Damme, 2005; Mogg et al., 2004). Within this context, 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 may be essential for survival in a hostile environment with a high risk for re-traumatization. Once a stimulus is categorized as threatening, however, further attention allocation towards the stimulus and a more detailed sensory processing is not necessary and might even be obstructive for the initiation of a flight reaction. This idea is consistent with the finding of reduced activity in visual cortical areas averaged across the first 4 seconds of aversive picture presentation (Catani, Adenauer, et al., 2009), whereas increased activity was generally found for the immediate event-related activity in PTSD (Karl et al., 2006; Metzger, Gilbertson, & Orr, 2005).

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 to neutral pictures in an event-related (ERF) field study with PTSD subjects. ERFs are the magnetic counterpart of event related potentials and allow studying brain cortical activity with a high temporal and spatial resolution.

To allow a comparison with the results of recent electrophysiological studies using emotional pictures as stimuli, we adhered to the standard procedure of presenting three categories of images: pleasant, unpleasant, and neutral. This procedure allows the determination of the specificity of the emotion-related effects with regard to the valence (positive vs. negative) of stimuli. Several ERP studies using the same stimulus material demonstrated that the brain systematically differentiates emotionally significant from affectively neutral visual inputs (P. J. Lang, Bradley, & Cuthbert, 1998a; H. Schupp et al., 2006).

We expected that PTSD patients would show an increased neuronal excitation following aversive stimulation in a cortical component of the fear-processing network, i.e. the ventral prefrontal cortex. This region plays a role in affective stimulus categorization and an increased reaction towards threat cues within 300 ms after stimulus onset has been shown (Kawasaki et al., 2001; Junghöfer et al., 2003). Following 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 the psychiatric diagnosis PTSD, three groups of participants were included in the experiment: PTSD subjects, Trauma Controls 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. The most common traumatic event was related to war and persecution and included torture experiences.

4.3 Methods

4.3.1 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 and co-workers (Catani, Adenauer, et al., 2009). Because of the exclusion of a few subjects due to bad 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 means of the Life Events Checklist of the Clinician Administered PTSD Scale, CAPS (Blake et al., 1995) and the vivo Checklist of War, Detention, and Torture events (Vivo, 2006). The Clinical Administered PTSD Scale (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. (Sheehan et al., 1998). The Hamilton Depression Rating Scale, HDRS (J. B. Williams, 1988). was used to assess severity of depressive symptoms. There was no significant group difference with respect to current psychoactive medication, except for antidepressants (eight people in the PTSD group, compared to two in the Trauma Controls, and none in the Unexposed group). Descriptive data as well as significant group differences in demographic and clinical variables are presented in table 1.

4.3.2 Stimuli and Presentation Procedure

A total of 75 colored pictures were chosen from the International Affective Pictures System (P. J. Lang et al., 2005). The pictures were divided according to hedonic valence and emotional arousal: 25 aversive (e.g., mutilations, assaults, weapons, etc.), 25 pleasant (e.g., sports, happy couples, children, etc.) and 25 neutral pictures (e.g., neutral faces, household objects, landscapes, etc.). These three categories differed significantly in terms of their normative valence ratings (pleasant: 7.4, neutral: 4.9, aversive: 2.4). While normative arousal ratings did not differ for pleasant and aversive contents, mean arousal levels for both emotional categories were significantly higher compared to neutral contents (pleasant: 5.6, neutral: 2.9, aversive: 5.8). Color spectra, contrast, and brightness of the pictures were matched across all three categories. Pictures were presented in a pseudo-random order using a video projector (JVC^{TM}, DLA-G11E) on a grey plastic screen that was attached to the ceiling of the MEG chamber.

Since the design of the study included the analysis of the steady state signal evoked by the emotional stimuli (Catani, Adenauer, et al., 2009), the pictures were presented in a flickering mode of 10 Hz for 4 seconds. During the inter-stimulus interval that varied randomly between 6 to 8 seconds, a black fixation cross was presented.

4.3.3 Procedure

Clinical interviews with trauma-exposed participants were carried out one week before MEG recording in order 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. Subsequently, participants were familiarized with the MEG chamber and

Table 4.1: Demographic and clinical characteristic of the three participant groups.

		PTSD (n=36)	Trauma Controls (n=21)	Unexposed (n=16)
Demographic Data				
Sex				
female	*N (%)*	15 (41.7)	13 (57.1)	9 (56.3)
male	*N (%)*	21 (58.3)	9 (42.9)	7 (43.8)
Age	*M (SD)*	33.6 (10.0)[a]	31.4 (11.2)	26.0 (6.6)[b]
Regions of Origin				
Middle East	*N (%)*	19 (52.8)[a]	8 (38.1)	6 (37.5)[b]
The Balkans	*N (%)*	3 (8.3)	6 (28.6)	9 (56.3)
Caucasus	*N (%)*	2 (5.6)	0	0
Asia	*N (%)*	3 (8.3)	3 (14.3)	0
Africa	*N (%)*	9 (25.0)	4 (19.1)	1 (6.3)
Clinical Data				
Events				
Nr. Traumatic Events				
CAPS Event-Types	*M (SD)*	7.0 (2.1)[a]	5.6 (1.6)[b]	1.6 (1.0)[c]
Vivo Checklist				
Nr. War & Torture-Types	*M (SD)*	10.9 (5.8)[a]	4.1 (5.4)[b]	0.5 (1.1)[c]
Clinical Symptoms				
CAPS Score	*M (SD)*	80.5 (16.6)[a]	13.6 (17.4)[b]	0.6 (2.3)[c]
Intrusions Score	*M (SD)*	26.6 (7.2)[a]	5.0 (7.1)[b]	0.1 (0.3)[c]
Avoidance Score	*M (SD)*	28.4 (8.2)[a]	4.8 (6.4)[b]	0.3 (1.3)[c]
Arousal Score	*M (SD)*	25.4 (5.9)[a]	3.8 (5.2)[b]	0.3 (1.0)[c]
Comorbid Disorders (M.I.N.I. Diagnoses)				
MD current	*N* (%)	27 (75)[a]	2 (9.5)[b]	0[b]
Dysthymia	*N (%)*	3 (8.3)	2 (9.5)	0
HDRS Score	*M (SD)*	25.6 (7.7)[a]	7.3 (7.6)[b]	1.4 (2.2)[c]

Note: For pair-wise group comparisons of continuous variables, Mann-Whitney U Tests were used; differences of categorical variables were evaluated by applying χ^2-Tests for independence. Different indices (a, b, c) indicate statistical difference ($p < .05$) between the reported results.

an informed consent form was signed. Subjects were seated in a magnetically shielded chamber and their head shapes were digitized with a Polhemus 3 Space Fasttrack (Polhemus, Colchester, VT, USA). Five index points were determined to calculate the relative head position within the MEG helmet for source analysis. Participants were instructed to avoid eye movements and eye blinks during picture presentation. After MEG recordings, subjects rated each of the 75 affective pictures regarding emotional valence and arousal using the Self-Assessment Manikin (SAM) self-report scale.

4.3.4 MEG Recording and Preprocessing

MEG was recorded continuously with a digitization rate of 678.17 Hz using a 148-channel whole head magnetometer (MAGNES^{TM} 2500 WH, 4D Neuroimage, San Diego, USA). A band-pass filter of 0.1–200 Hz was applied online. For artifact control, EOG and ECG were recorded with a SynAmps amplifier (Neuroscan^{TM}) using Ag/AgCl electrodes. Offline, MEG data were visually inspected for movement artifacts. 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 using the algorithm implemented in BESA^{TM} software (Berg & Scherg, 1994). The MEG data were digitally filtered between 1 Hz high-pass (6 dB/octave) and 25 Hz low-pass (24 dB/octave). Finally, MEG data were averaged for picture category (pleasant, neutral, and aversive).

4.3.5 Source Analysis

Using the Matlab-based software EMEGS© (Junghöfer & Peyk, 2004), 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 (Hämäläinen & Ilmoniemi, 1994). Calculation of the L2 minimum norm was based on a one-shell spherical head model with 2 (azimuth and polar direction) $\times$ 197 evenly distributed dipolar sources. A shell radius of 6 cm was chosen as the best tradeoff between depth sensitivity and spatial resolution (Hauk, 2004). Prior to calculating the L2 minimum norm estimate, sensor data were baseline-corrected (500 ms pre-stimulus). Estimated dipole strength was averaged for each group separately. Because the aim of this analysis was to investigate temporally early picture processing, and to avoid contamination by the gradually developing steady-stated response triggered by the flickering stimulation, analyses were limited to the first 300 ms after stimulus onset.

Time windows and regions of interest for the statistical analyses were determined in two steps. At first, time windows were selected on the basis of the time course of the global field power of the minimum norm, which gives the overall neural activity

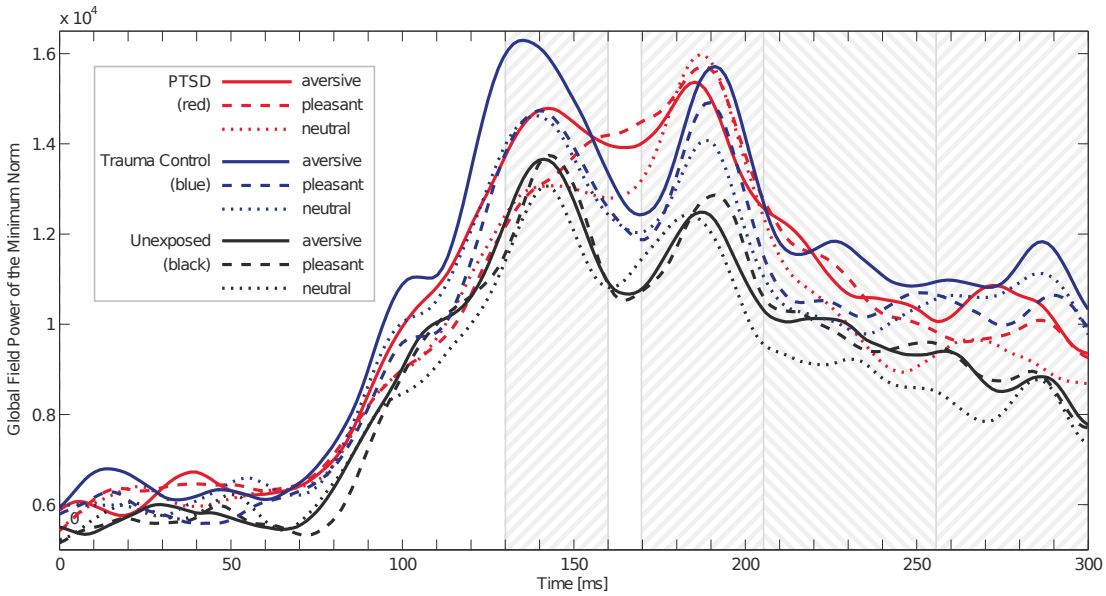

Figure 4.1: Global Field Power of the magnetic field obtained at 197 dipoles for pleasant, neutral, and aversive pictures of each group separately. Shaded regions depict time windows of interests determined from the component structure of the data.

across all dipoles (figure 1). We identified time windows with a minimum duration of 30 ms that showed an apparent group difference of the emotion modulation. As the main hypothesis was related to the response towards aversive stimuli, we focused on the unpleasant-neutral contrast for this screening. Pleasant stimuli served to establish the valence but not arousal specificity of expected cortical effects of aversive pictures. Four time windows were determined around the four obvious activity peaks (130–160 ms, 170–205 ms, 206–256 ms, 257–300 ms after stimulus onset).

Secondly, for each group and each time window condition differences (aversive-neutral) were projected on the surface of a 3D-model of a standard brain. Spatial regions of interests (ROIs) were selected for each time window on the basis of a visual inspection of valence-dependent activation differences within the three groups of participants. Because visual inspection suggested hemispheric differences in effects, a factor Hemisphere was included in the statistical analysis. To avoid false positives, only regions where the spatial extent of the aversive-neutral contrast comprised at least 8 adjacent dipoles were selected for further analysis. Figure 2 provides a schematic layout of the dipole groups used for statistical analyses.

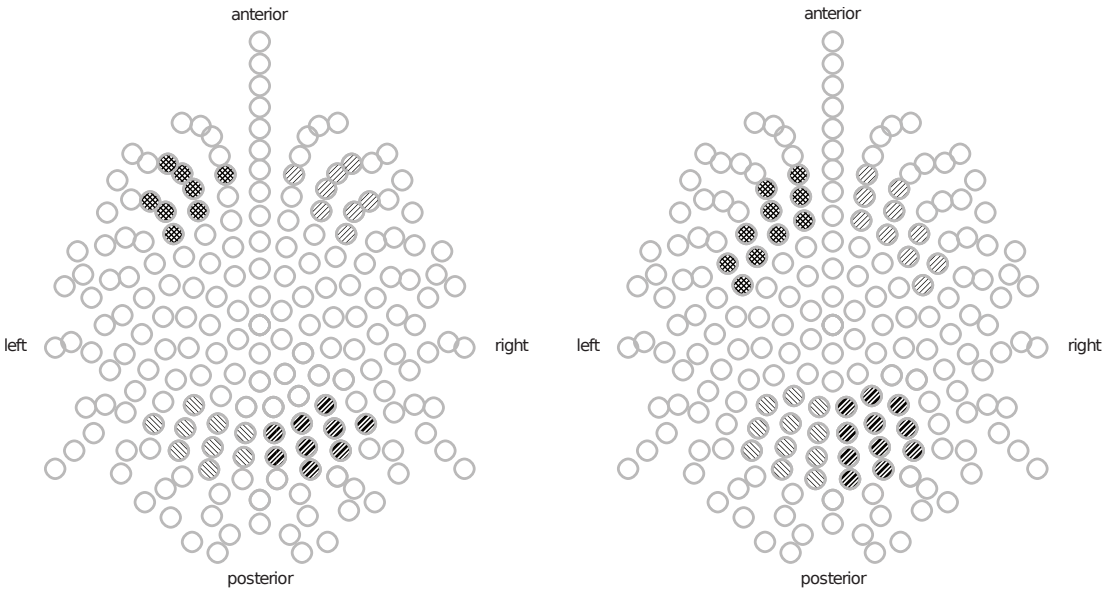

Figure 4.2: Schematic layout of the dipole distribution used for the L2 minimum norm estimate. Dipole groups used for the statistical analysis are marked.

4.3.6 Statistical Analysis

SAM pleasure and arousal ratings were analyzed using repeated-measures ANOVA with Group (Unexposed, Trauma Controls, PTSD) as the between factor and Category (pleasant, neural, aversive) as the within factor. Activity at ROIs was analyzed with repeated-measures ANOVAs with Group as the between factor and with Category as well as Hemisphere (left, right) as the within factors. Since our main interests centered on group-specific differences in affective picture processing, only significant Group $\times$ Category or Group $\times$ Category $\times$ Hemisphere interactions within the ROIs were further analyzed. For a further exploration of the interaction effects, repeated measures ANOVAs were calculated for each group separately. Greenhouse-Geisser's corrections of the degrees of freedom were used where appropriate, and the associated epsilon and adjusted p-values are reported. Statistically significant interactions were further investigated by means of post-hoc comparisons using the Tukey's HSD test.

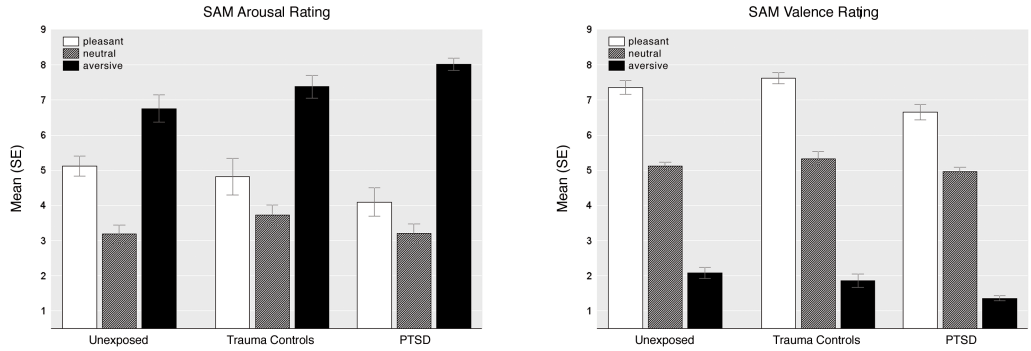

Figure 4.3: Means of SAM arousal (left) and SAM valence (right) ratings of the three groups. Error bars indicate standard errors.

4.4 Results

4.4.1 Subjective Ratings of Affective Stimuli

SAM arousal ratings revealed a significant interaction effect of Group × Category ($F(4, 106) = 5.48$, $p < .001$, $\varepsilon = .88$) suggesting PTSD patients rated pleasant pictures as less arousing and unpleasant pictures as more arousing than the unexposed group. Post-hoc analyses showed, however, a significant effect of Category (all comparisons $p < .001$) but did not confirm significant group differences. Analyses of the SAM valence ratings showed a significant main effect of Group ($F(2, 53) = 9.34$, $p < .001$). PTSD patients rated all pictures as less pleasant compared to the other groups (Tukey's HSD $p < .001$ for the comparison PTSD vs. Trauma Controls and $p = 0.007$ for Unexposed vs. PTSD) (see figure 3). After the MEG recordings, some participants were fatigued and had difficulties to concentrate on the subjective ratings of the pictures. Therefore, only 14 Unexposed, 16 Trauma Controls, and 26 PTSD participants completed SAM ratings.

4.4.2 Minimum Norm Estimates

Whereas main effects of picture category were present in all selected time windows, significant Group × Condition × Hemisphere interactions were only found within the time windows of 130–160 ms and 206–256 ms.

For the identified ROI in the ventral prefrontal cortex at 130–160 ms this interaction reached $F(4, 140) = 2.47$, $p = .048$. Individual ANOVAs for each group revealed a significant effect of Category only in the PTSD group for the right hemisphere ($F(2, 70) = 8.43$, $p < .001$). PTSD patients showed significantly enhanced dipole source

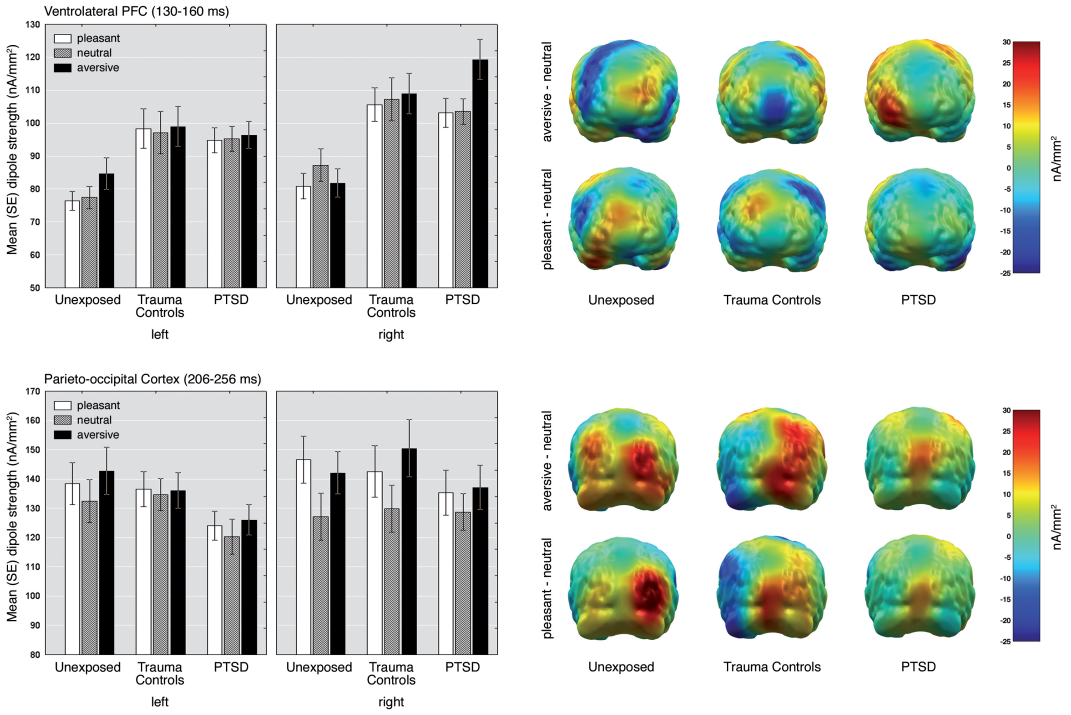

Figure 4.4: Brain maps showing source activity of the condition contrasts (aversive- neutral and pleasant-neutral) for the three groups (right). Repeated measures ANOVA depict the statistical differences in the cortical activity within the selected ROIs (left).

strength towards aversive pictures compared to neutral, as well as to pleasant pictures (Tukey's $p = .002$ for both comparisons). There was no significant effect of Category in any of the two control groups (see figure 4).

Within the time period of 206–256 ms, a significant interaction of Group × Category × Hemisphere ($F(4, 140) = 2.50$, $p < .046$) was found in the parieto-occipital ROI. Here, individual ANOVAs revealed a significant Category effect in the right hemisphere only in the Trauma Controls ($F(2, 40) = 14.36$, $p < .001$) and in the Unexposed group ($F(2, 30) = 7.38$, $p = .003$). Both groups showed significantly higher dipole source strength towards emotional pictures compared to neutral content (Trauma Controls: Tukey's $p < .001$ for aversive vs. neutral and $p = .006$ for pleasant vs. neutral; Unexposed Group: $p = .026$ for aversive vs. neutral and $p = .003$ for pleasant vs. neutral). By contrast, PTSD patients did not show any significant Category effect at this processing stage (see figure 4).

4.5 Discussion

As predicted, we found evidence for a biphasic cortical reaction in patients with PTSD compared to trauma exposed and non-trauma exposed healthy control subjects within the first 300 ms of visual processing. This response consists of an augmentation of reactivity towards aversive stimuli in prefrontal areas followed by a decrease of the affective modulation in the parieto-occipital cortex. This finding is consistent with the hypothesis of a vigilant-avoidant reaction pattern to threat cues in anxiety disorders. Our findings indicate that PTSD affects specialized mechanisms of early stimulus classification. As early as 130–160 ms after stimulus onset, PTSD subjects showed an exaggerated prefrontal neural response to emotional stimuli (see figure 4). Notably, this effect was specific for unpleasant stimuli. This result confirms a previous study by Junghöfer et al. (2003) who found a similar early response to aversive pictures in PTSD in orbitofrontal regions. Recent research using single cell recordings indicates that ventral prefrontal neurons provide a rapid affective categorization of visual stimuli within this time window (Kawasaki et al., 2001). These findings are consistent with the idea of a rapid threat detection mechanism that occurs independently of a detailed visual stimulus analysis (LeDoux, 2000). Notably, this mechanism not only involves subcortical brain structures, but also ventral prefrontal cortical areas (B. J. Liddell et al., 2005; B. Liddell, Williams, Rathjen, Shevrin, & Gordon, 2004; L. Williams et al., 2006).

The prefrontal hyperactivation to aversive stimuli found in our study, however, seems to contradict brain imaging studies with PTSD patients that generally demonstrate the opposite effect, i.e. a prefrontal hypoactivation rather than hyperactivation in response to aversive stimuli (Shin et al., 2006). An explanation for the diverse findings of EEG and fMRI research could be that the over-responsiveness found in the EEG signals was only transient and generally lasted no longer than 30–80 ms. Such a process can hardly be detected with the fMRI, which is restricted by a much lower temporal resolution. Some authors, however, suggested that it is possible to trace rapid transient neural processes with the fMRI by presenting stimuli subliminally. Following this logic, a recent study employed a nonconscious presentation of affective faces to investigate rapid brain responses in PTSD (R. Bryant et al., 2008). In contrast to the findings using overt presentation, and in agreement with our study, the authors found an increased prefrontal activity following affective stimulation in PTSD patients. The early prefrontal activity might have been caused by an excitatory bottom-up influence of the amygdala on the prefrontal cortex (B. Liddell et al., 2004; Gilboa et al., 2004), which is consistent with a rapid initiation of a widespread neuronal fear network.

Consistent with our hypothesis, we found that the prefrontal hyperactivation in PTSD was followed by an attenuated activity towards high-arousing stimuli in the parieto-occipital cortex in a later time window (206–256 ms). This confirms the results of recent ERP studies that also found reduced posterior ERP signals in response to affective faces (Felmingham et al., 2003) or affective pictures (Weber et al., 2009) in

patients with trauma-related psychopathology. This finding, however, stands in contrast with other ERP studies that found increased event-related electrical activation in PTSD compared to healthy controls in posterior sites of the brain in response to threatening visual stimuli (Attias, Bleich, Furman, & Zinger, 1996; Bleich, Attias, & Furman, 1996). A likely explanation for the discrepant findings might be that the posterior reaction to aversive stimuli depends on stimulus intensity and perceived self-relatedness. In two previous studies, for example, PTSD participants showed a continuously decreasing brain response to tones as they were presented with an increasing intensity (Paige, Reid, Allen, & Newton, 1990; Lewine et al., 2002). It could be speculated that PTSD subjects respond with enhanced brain activity towards aversive stimulation up to a certain threshold. Beyond this threshold, neural processes reverse as they instigate a state of protective inhibition of cortical activity in order to protect the cortex from over-stimulation (Buchsbaum & Pfefferbaum, 1971). Even though the pictures used in our study were not deliberately chosen to be trauma-related, many of the pictures might have triggered memories related to the individual traumatic experiences in our sample and thus exceeded the level of general aversive stimulation.

Whereas the early hyperactivation was specific for aversive stimuli, the later disengagement involved negative as well as positive stimuli. This finding is in line with the other studies that found a reduced cortical response towards arousing stimuli in traumatized subjects (Mogg et al., 2004; Metzger et al., 2005). It seems that the neuronal avoidant reaction includes all types of arousing stimuli, which corresponds to the unspecific emotional numbness in PTSD subjects, which is a common symptom of the disorder.

The so-called hypervigilance-avoidance pattern found in the present study is characterized by an initial attentional vigilance followed by an attentional avoidance, which is a finding that has already been demonstrated for anxious participants in a recent ERP study by Holmes, Nielsen, and Green (2008). The biphasic process allows for a rapid detection of threat cues that initiates an immediate flight or fight response. It might therefore reflect an adaptation of the cortical processing in individuals who live in a threatening or traumatizing environment. Once the stimulus has been classified as dangerous, further and more detailed analyses might not be necessary, thus leading to a reduced attention allocation. In agreement with this supposition, a previous study showed that the avoidant reaction of the visual cortical response remains for at least 4 seconds (Catani, Adenauer, et al., 2009). Further evidence comes from two recent studies that revealed a significant tendency of maltreated children with PTSD and subjects with a generalized anxiety disorder to shift attention away from angry faces (Pine et al., 2005; Monk et al., 2006). Notably, this tendency was associated with greater right ventrolateral prefrontal cortex activation (Monk et al., 2006).

The present study chose a sample of severely traumatized subjects (victims of war and torture) to study the correlates of trauma-related psychopathology. While the intense trauma history as well as the high level of psychopathology increased the probability of

finding neuronal correlates, several characteristics of the sample impair the unequivocal interpretation of the results. As there were substantial between-group differences in comorbid disorders, in particular depression, our results reflect the correlates of trauma-related psychopathology rather than solely PTSD. This problem, however, is inherent in most PTSD research and can, therefore, not be accounted for by statistical analyses (G. Miller & Chapman, 2001). By stimulating with flickering pictures, we used an unusual mode of presentation. While this stimulation allows the identification of sustained effects by analyzing the steady-state signal (Catani, Adenauer, et al., 2009) as well as the immediate effects based on the ERF signal, it is not clear how the presentation affects the early potentials in comparison to a constant stimulation. As we restricted the ERF analysis on the first 300 ms, however, there is no reason to assume stimulation frequency of 10 Hz would have dramatic effects on the data.

Whereas the results of the study are consistent with an attentional bias to threat cues, we cannot determine the specificity of the effect. Aversive stimuli were selected to be highly arousing and unpleasant, which was confirmed by the participants' ratings. Although it seems likely that high arousing unpleasant stimuli are predominantly threatening, we cannot specify whether the effect is exclusively related to fearful stimuli rather than stimuli evoking other unpleasant emotions including disgust. Taken together, our findings contribute to the integration of seemingly contradictory findings in the assessment of alterations of brain responses to threatening stimuli in PTSD. The commonly found opposing results of over- and under-responsiveness might reflect the correlates of at least two different processes that are temporally and spatially dissociated.

4.6 Acknowledgements

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5 Pattern of cortical activation during processing of aversive stimuli in traumatized survivors of war and torture

5.1 Abstract

Posttraumatic stress disorder has been associated with an altered processing of threat-related stimuli. In particular, an attentional bias towards threat cues has been consistently found in behavioral studies. However, it is unclear whether increased attention towards threat cues translates into preferential processing as neurophysiological studies have yielded inconsistent findings. The aim of the present study was to investigate the neocortical activity related to the processing of aversive stimuli in patients with PTSD.

36 survivors of war and torture with PTSD, 21 Trauma Controls and 20 Unexposed Subjects participated in a visual evoked magnetic field study using flickering pictures of varying affective valence as stimulus material. Minimum norm source localization was carried out to estimate the distribution of sources of the evoked neuromagnetic activity in the brain.

Statistical permutation analyses revealed reduced steady-state visual evoked field amplitudes over occipital areas in response to aversive pictures for PTSD patients and for Trauma Controls in comparison to unexposed subjects. Furthermore, PTSD patients showed a hyperactivation of the superior parietal cortex selectively in response to aversive stimuli, which was related to dissociative symptoms as well as to torture severity.

The results indicate a different pattern of cortical activation driven by aversive stimuli depending on the experience of multiple traumatic events and posttraumatic stress disorder. Whereas a decreased visual processing of aversive stimuli seems to be associated with trauma exposure in general, the superior parietal activity might represent a specific process linked to the diagnosis of PTSD.

5.2 Introduction

Current etiological models of posttraumatic stress disorder (PTSD) have identified the altered processing of threatening stimuli, in particular stimuli that are reminiscent of the traumatic experiences, as a core feature of PTSD (A. Ehlers & Clark, 2000).

Consistent with this assumption, several studies on information processing in PTSD have consistently found an attentional bias to threat-related or trauma-relevant stimuli (Buckley et al., 2000; McNally, Kaspi, Riemann, & Zeitlin, 1990; McNally et al., 2000) in this population. In particular, it has been shown that PTSD patients are more easily distracted by task-irrelevant aversive stimuli, regardless of the relevance of these stimuli to the trauma. This finding seems to indicate a preferential detection and encoding of aversive stimuli in PTSD patients. However, it is unclear whether the increased task interference caused by distracting aversive stimuli is brought about by enhanced stimulus processing or by other cognitive processes that are triggered by the threatening stimuli.

The use of neurophysiological methods, in particular electroencephalographic procedures with a high temporal resolution could help to understand alterations in the early processing of threatening cues in PTSD. Karl et al. (2006) have recently reviewed studies examining event-related potentials in PTSD and concluded that this disorder is typically associated with alterations in the amplitude and latency of ERPs indicating that changes in information processing can accompany PTSD. More specifically, Attias and co-workers used an EEG oddball paradigm with Israeli combat veterans with and without PTSD (Attias et al., 1996; Bleich et al., 1996). They found indicators for a preferential processing of trauma-related stimuli within the first 500 ms after stimulus onset, as only PTSD patients showed enhanced P3 and N1 amplitudes to non-target combat-related pictures. A similar effect could be demonstrated for non-trauma related aversive stimuli (C. L. Ehlers et al., 2006). However, research in this field is limited and inconsistent, as some studies failed to demonstrate enhanced event-related components towards traumatic targets in PTSD patients (Metzger, Orr, Lasko, & Pitman, 1997) or even found hyporesponsivity to threat cues in PTSD patients (Felmingham et al., 2003). Findings from studies with high- and low-anxiety individuals might help to resolve these conflicting findings as these studies indicate that the relationship between anxiety and the attentional processing of aversive stimuli changes within the early processing stages (Holmes et al., 2008; Rossignol, Philippot, Douilliez, Crommelinck, & Campanella, 2005). High anxiety, and possibly also PTSD, seems to be related with a potentiation of the initial threat evaluation but an attenuation of the later cognitive processing aversive stimuli (Holmes et al., 2008).

In the present study we wanted to examine neural correlates of sustained cortical processing of aversive stimuli within the first seconds after stimulus presentation. In particular, we wanted to find out whether PTSD is related to alterations in the processing of threat related pictures in cortical areas that are related to visual attention and processing. We applied magnetoencephalography (MEG) to measure steady-state visual evoked fields (ssVEFs) during the presentation of standardized affective pictures varying with respect to arousal (high and low) and valence (pleasant and unpleasant). SsVEFs are the neuromagnetic counterparts of steady-state visual evoked potentials (ssVEPs) and represent a continuous brain response elicited by a repetitive visual stim-

ulus presented at a predefined frequency (e.g., 10 Hz). The ongoing cortical oscillatory neuromagnetic responses have the same fundamental frequency as the driving stimulus (Regan, 1989). Past studies with healthy subjects have shown that highly arousing pictures generate greater ssVEFs or ssVEPs than neutral, low-arousing pictures mostly in occipital and parietal cortical networks (A. Keil et al., 2003; Kemp et al., 2002; Moratti et al., 2004) indicating the allocation of attentional resources to stimuli according to their respective affective significance. Recently, a study by Moratti and co-workers has demonstrated that the pattern of ssVEFs elicited by emotional pictures can discriminate between patients with major depressive disorder and healthy control subjects (Moratti et al., 2008).

In the present study, we were able to examine survivors of war and torture with a DSM-IV diagnosis of PTSD as well as a matched sample of refugees with similar ethnicities who had experienced traumatic experiences but did not fulfill criteria of PTSD. By comparing these two groups with healthy control subjects we aimed at distinguishing between effects related to trauma severity and those related to the presence of the diagnosis of PTSD. Given the inconsistent findings of previous research on the processing of threat-related stimuli in PTSD, the main aim of the present study was to find out whether PTSD patients in comparison to trauma-affected subjects without PTSD and healthy individuals would show an increase or decrease in occipital-parietal neocortical activity related to the processing of aversive pictures, and whether the spatial pattern of activation would differ between groups. In agreement with existing research on neural correlates of affective visual processing (A. Keil et al., 2003; Kemp et al., 2002; Moratti et al., 2004), activation of visual cortical areas is seen as reflecting attention allocation towards emotionally and motivationally salient stimuli (P. J. Lang et al., 1997). Finally, we wanted to explore whether trauma-related variables (such as the amount of previously experienced war and torture experiences) and clinical variables (such as PTSD severity, co-morbid depressive symptoms, and dissociative features) are related to source activity elicited by aversive stimuli.

5.3 Methods

5.3.1 Subjects

57 war and torture-exposed participants and 20 comparison individuals with comparable ethnicities participated in the study. Trauma-exposed participants were asylum seekers with a history of persecution, war and torture who came for treatment or expert opinion to the Psychotrauma Research and Outpatient Clinic for Refugees, located at the Centre for Psychiatry, Reichenau, Germany. The trauma-exposed group was further subdivided according to PTSD diagnosis. The PTSD Group was composed of 36 subjects who fulfilled DSM-IV criteria for current PTSD, whereas 21 survivors of war and torture experiences did not meet PTSD criteria (Trauma Controls). Comparison partic-

ipants were recruited by searching for migrants born in conflict regions with hardly any past traumatic experiences by announcements on campus bulletin boards (Unexposed Controls).

All subjects underwent an extensive clinical examination which included a thorough assessment of traumatic experiences by means of the vivo checklist of war, detention, and torture events (Vivo, 2006). Common traumatic experiences reported by refugees included bombings, seeing dead bodies in the street, being tortured in prison, or being beaten up by the police. A broader range of traumatic event types, including car accidents and criminal attacks, were assessed using the event checklist of the Clinician Administered PTSD Scale, CAPS (Blake et al., 1995). Standardized clinical instruments were used for the assessment of DSM-IV diagnoses: The CAPS for the diagnosis and quantification of PTSD and related dissociative features, the Mini International Neuropsychiatric Interviews, MINI (Sheehan et al., 1998) for diagnoses of DSM-IV axis one disorders, the Hamilton Depression Rating Scale, HDRS (J. B. Williams, 1988) for determining the severity of depressive symptoms, and the Screening for Somatoform Symptoms-7, SOMS-7, (Rief & Hiller, 2003), for the assessment of somatic problems.

The resulting demographic and clinical characteristics of the three groups and significant group differences are listed in table 1. All participants provided written informed consent and the procedures were approved by the ethics committee of the University of Konstanz.

5.3.2 Stimuli

Seventy-five colored pictures were chosen on the basis of their normative ratings from the International Affective Pictures System (P. J. Lang et al., 2005). Of these, 25 pictures presented unpleasant, events (e.g., mutilations, assaults, dead bodies, etc.), 25 pictures presented pleasant events (e.g., sports, erotic couples, children, etc.) and 25 presented neutral events (e.g., neutral faces, household objects, etc.) Amongst the unpleasant pictures, the majority of stimuli was threat-related with about one third depicting human assaults or aimed guns, another third showing mutilations or dead bodies. Scenes with soldiers or police officers were presented on three slides, and on another three, angry and sad faces were shown. The three categories differed significantly from each other in IAPS normative valence ratings (pleasant: 7.4, neutral: 4.9, unpleasant: 2.4). Normative arousal ratings did not differ for pleasant and unpleasant contents, but mean arousal levels for both emotional categories were significantly higher than for neutral contents (pleasant: 5.6, neutral: 2.9, unpleasant: 5.8). Brightness, contrast and color spectra of the stimuli were matched across picture categories. Pictures were presented using a video projector (JVC^{TM}, DLA-G11E) with a refresh rate of 100 Hz on a white plastic screen attached to the ceiling of the room. Pictures subtended a visual angle of 10 ° horizontally and 8 ° vertically to either side from the centre of the screen. In each trial, one picture was presented in a flickering mode of 10 Hz for 4 seconds,

Table 5.1: Demographic and clinical characteristic of the three groups.

Variable	PTSD Group (n=36)	Trauma Controls (n=21)	Unexposed Group (n=20)
mean age in years (SD)	33.6 (10.0)	29.9 (9.6)	27.8 (9.4)
mean school educ. in years (SD)	8.2 (3.3)	11.8 (1.8)	12 (2.0)
N females (%)	15 (38.5)	13 (61.9)	11 (55.0)
region of origin, N (%)			
Africa	9 (25.0)	4 (19.1)	3 (15.0)
South Asia	0	1 (4.8)	0
Caucasus	2 (5.6)	0	0
Middle East	22 (61.1)	11 (52.4)	5 (25.0)
Balcans	3 (8.3)	5 (23.8)	12 (60.0)
Europe	0	0	0
safe asylum status, N (%)	4 [a] (11.1)	16 [b] (76.2)	18 [b] (90.0)
Trauma load (mean number (SD))			
CAPS event types	7.0 [a] (2.1)	5.9 [a] (1.4)	1.8 [b] (0.9)
war and torture event types	10.9 [a] (5.7)	4.1 [b] (5.4)	0.6 [c] (1.3)
CAPS PTSD symptom score, mean (SD)	80.5 [a] (16.6)	15.7 [b] (21.3)	3.5 [c] (8.8)
N with dissociative symptoms (%)	12 [a] (35.3)	2 [b] (9.5)	0 [b]
M.I.N.I. diagnoses, N (%)			
MD current	27 [a] (75)	2 [b] (9.5)	2 [b] (10.0)
Dysthymia	3 (8.3)	2 (9.5)	2 (10.0)
mean HDRS score (SD)	25.6 [a] (7.7)	7.3 [b] (7.5)	3.9 [b] (6.7)
mean SOMS score (SD)	27.5 [a] (11.9)	8.7 [b] (10.4)	4.9 [b] (7.2)
Medication, N (%)			
Pain killers	20 [a] (55.6)	7 [b] (33.3)	2 [b] (10.0)
Anxiolytics	2 (5.6)	0	0
Hypnotics	3 (8.3)	1 (4.8)	0
Antidepressants	8 (22.2)	2 (9.5)	0
Neuroleptics	2 (5.6)	1 (4.8)	0

Note: Indices represent the results of pair-wise group comparisons using the Mann-Whitney-U-tests for continuous variables and the χ^2 test for dichotomous variables; different indices indicate significant differences on $p < .05$

resulting in 40 on/off cycles (same picture shown and not shown) of 50 milliseconds each. The inter-trial interval varied randomly between 6 to 8 seconds and consisted of the presentation of a grey screen with a fixation cross to aid participants in maintaining gaze on the center of the screen.

5.3.3 Procedure

MEG recording was carried out within one week after clinical examination. Upon arriving at the laboratory, participants were familiarized with the MEG chamber and an informed consent form was signed. Handedness was determined using the Edinburgh Inventory (Oldfield, 1971). For artifact control, the electro-oculogram and electrocardiogram were recorded. Subjects were seated in a magnetically shielded chamber and their head shapes were digitized with a Polhemus 3 Space Fasttrack (Polhemus, Colchester, VT, USA). Five index points (left and right periauricular points, nasion, a pseudo-Cz and pseudo-inion point at the forehead) were determined to calculate the relative head position within the MEG helmet for source analysis. During MEG recording, a video camera monitored subjects' behavior and assured compliance throughout the experiment.

Participants were instructed to avoid eye movements and eye blinks during picture presentation. After MEG recordings, subjects rated each of the 75 affective pictures regarding emotional valence and arousal using the Self-Assessment Manikin self-report scale (M. Bradley & Lang, 1994).

5.3.4 MEG Recording and Data Preprocessing

MEG was recorded continuously and digitized at a rate of 678.17 Hz using a 148-channel whole head magnetometer (MAGNES^{TM} 2500 WH, 4D Neuroimage, San Diego, USA). A band-pass filter of 0.1–200 Hz was applied online. EOG and ECG were recorded with a SynAmps amplifier (Neuroscan^{TM}) using Ag/AgCl electrodes.

Offline, MEG data were visually inspected for movement artifacts. 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 using the algorithm implemented in BESA^{TM} software (Berg & Scherg, 1994). This method uses the vertical EOG to determine the topography of blinks based on the first component of a principle component analysis (PCA) of the average blink activity. The correction of blinks is then carried out by applying the surrogate MSEC methods as described by Berg and Scherg (1994). The MEG data were digitally band-pass filtered between 1 Hz and 25 Hz (slopes: 6 and 24 dB/octave, respectively). Trials containing maximum amplitudes above 3.5 pT were discarded from further analysis. Finally, MEG data were averaged for picture category (pleasant, neutral and unpleasant) over 5000 ms (500 ms baseline, 4000 ms stimulus

presentation, 500 ms post stimulus).

For each category average, the 10 Hz Fourier component was derived using a moving window averaging procedure (A. Keil et al., 2003). To avoid contamination of results with the event related early activity, the initial 500 ms of the picture presentation interval were excluded. The resulting 500–4000 ms post stimulus part of each epoch was baseline-corrected (500 ms pre-stimulus) and used for further analysis. A 400-ms window containing four cycles of the 10 Hz flickering stimuli was shifted in steps of 100 ms (one cycle) across the epoch, and the magnetic field data within the shifting windows in the time domain were further averaged. The resulting four cycles per category, subject, and MEG channel were submitted to the fast Fourier transform (FFT) technique (Bickford et al., 1971). The real and the imaginary parts of the 10 Hz Fourier component were extracted for further analysis.

5.3.5 Source Analysis

Using the Matlab-based software EMEGS© (Junghöfer & Peyk, 2004) the distribution of likely generators of the neuromagnetic activity was estimated by calculating L2-minimum norm solutions (Hämäläinen & Ilmoniemi, 1994). Calculation of the L2 minimum norm was based on a one-shell spherical head model with 2 (azimuth and polar direction) $\times$ 197 evenly distributed dipolar sources. A shell radius of 6 cm was chosen as the most preferable trade-off between depth sensitivity and spatial resolution (Hauk, 2004). The regularization parameter λ was .02 and thus identical across all subjects and conditions. For visualization purposes, the estimated neural activities were projected onto the surface of a smoothened standard brain. Minimum norm estimation was calculated in the frequency domain by submitting the real and the imaginary parts of the 10-Hz Fourier component to the minimum norm estimates (MNE) analysis (Jensen & Vanni, 2002) and by using the root sum square of the 2 Fourier parts as an estimate of absolute power. As an example, mean activation towards unpleasant slides separately for each group is shown in figure 1.

5.3.6 Statistical Analysis

The main aim of the statistical analysis of MNE data was to find differences between the three subjects groups with respect to the processing of aversive stimuli. To determine the valence specificity of this effect, we repeated the same analysis for the pleasant stimulation. To control for different levels of overall stimulus-driven activity, source activity related to neutral pictures was subtracted from activity in response to aversive pictures ('unpleasant minus neutral' difference) and to pleasant pictures ('pleasant minus neutral' difference) for each subject. The resulting condition contrast maps were averaged across groups, resulting in two condition contrast maps per group. For both types of contrast map, three pair-wise statistical group comparisons (PTSD vs. Trauma

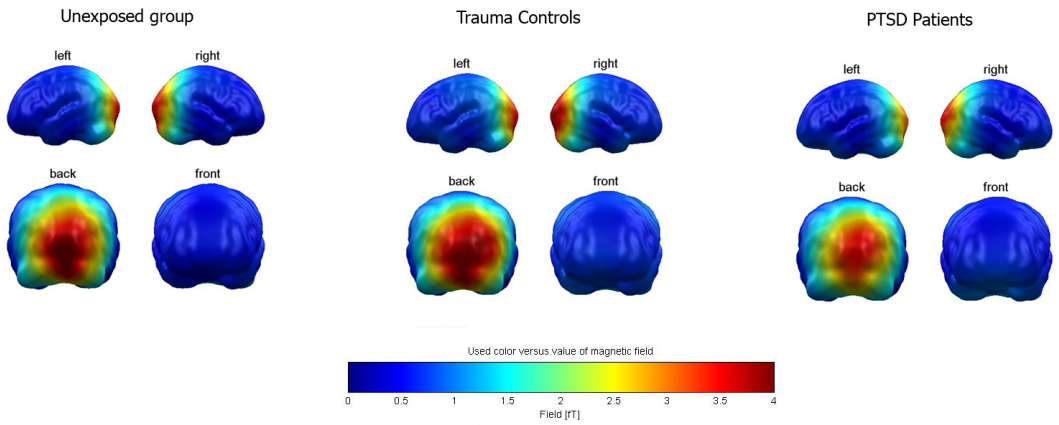

Figure 5.1: Topographical brain maps showing cortical source activity following the presentation of unpleasant slides, separately for each group.

Controls, PTSD vs. Unexposed and Trauma Controls vs. Unexposed) were carried out.

To cope with the high number of comparisons on dipole level without predetermining regions of interest, we applied permutation tests for the comparison of brain maps (Karniski et al., 1994). The advantage of the permutation test is that it does not require any a priori assumption about the distribution of the data, as it generates all possible permutations of the data to represent the data distribution. Given that permutation or randomization tests are able to cope with small and unequal samples in biomedical research, permutation tests are to be preferred to t or F tests when analyzing location differences (Ludbrook & Dudley, 1998). A previous MEG study investigating the processing of high-arousing pictures in depressive patients has also used permutation analyses to show differences in arousal dependent modulation of source strengths between depressive and healthy individuals (Moratti et al., 2008).

For each comparison, we determined cut-off values for significant group differences of the maps at single dipole locations based on 1000 draws. For each draw, the individual condition contrast maps were randomly exchanged between groups to generate data for a random group composition. The maximum as well as the minimum differences at all dipole locations obtained from each draw entered the distributions of 1000 maximum and minimum difference values. The upper and the lower critical values were determined as the 25th ($p < .025$) lowest and highest values in this distribution.

In table 2, upper and lower critical difference values for each pair-wise group comparison are listed. Values indicating a significant difference (smaller than the lower and higher than the upper critical values) were plotted onto the MNI brain to identify regions of interest (ROIs) associated with group differences in processing unpleasant as well as pleasant pictures. To allow a better understanding of group differences, t-tests

Table 5.2: Critical difference values with permutation $p < .025$ for paired group comparisons

	lower critical value	upper critical value
Activation for pleasant pictures (pleasant minus neutral)		
Patients minus Unexposed Group	-0.24	0.23
Patients minus Trauma Controls	-0.24	0.23
Trauma Controls minus Unexposed Group	-0.27	0.26
Activation for unpleasant pictures (unpleasant minus neutral)		
Patients minus Unexposed Group	-0.32	0.32
Patients minus Trauma Controls	-0.32	0.31
Trauma Controls minus Unexposed Group	-0.36	0.35

for independent samples were conducted for each pair-wise comparison with the difference values at ROIs for 'unpleasant minus neutral' and 'pleasant minus neutral' as independent variables.

Valence and arousal ratings were evaluated using repeated-measures ANOVA with group as the between factor and with picture category as the within factor. Greenhouse-Geisser corrections of the degrees of freedom were applied where appropriate. Statistically significant interactions were investigated by using Tukey HSD test for post-hoc evaluation of unequal sample sizes.

In addition, exploratory analyses were carried out to investigate the relationship between subjective picture ratings, clinical variables, and cortical activation patterns separately for each picture category. Spearman rank correlation coefficients were used for these analyses. Correlations between clinical scores (CAPS, HDRS, and SOMS-7) and activation towards unpleasant, neutral, and pleasant pictures at ROIs, were carried out with a combined group of PTSD patients and Trauma Controls since the Unexposed participants scored consistently low on all clinical instruments. The analysis of correlations between trauma load (number of torture events, number of war events, number of events listed in the CAPS) and cortical activation was accomplished with trauma-exposed subjects who reported at least one experience in the respective category.

To test whether the presence of dissociative symptoms in PTSD patients might be related to activation patterns towards unpleasant or pleasant visual stimuli, we subdivided the PTSD sample into a subgroup who did not report any dissociative symptom on the CAPS ($n = 22$) and another subgroup with patients who reported at least one dissociative symptom (reduction in awareness, derealization or depersonalization) in the last four weeks ($n = 12$). It is important to note that these subgroups did not differ with respect to gender, to the number of traumatic, war or torture events experienced, nor on PTSD symptom severity.

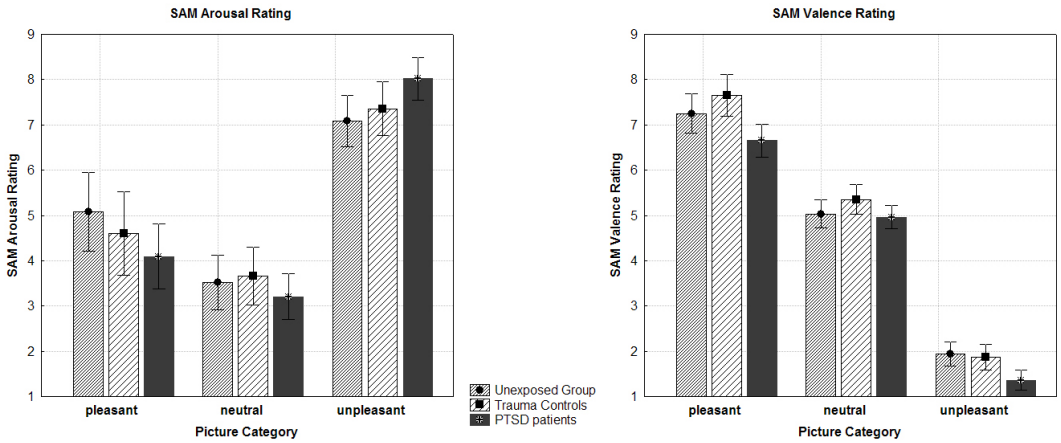

Figure 5.2: SAM Arousal and Valence ratings of the three subject groups with error bars indicating 95% confidence intervals. Post-hoc analyses showed that arousal ratings differed in relation to picture valence in the unexposed group. Here, unpleasant pictures were rated as more arousing compared to neutral ($p < .001$) as well as pleasant ($p < .001$) pictures. Pleasant pictures were rated as more arousing compared to neutral pictures ($p < .005$). Both, trauma controls and the patient group reported higher ratings for unpleasant pictures than for neutral ($p < .001$ for both comparisons) as well as for pleasant ($p < .001$ for both comparisons) pictures. However, these two latter groups did not differ between neutral and pleasant picture with respect to their subjective arousal rating. With respect to stimulus valence, PTSD patients rated pictures in general as less pleasant as compared to Trauma Controls ($p < .005$) as well as to the Unexposed Group ($p < .05$). There was no difference between the non-PTSD samples with respect to their subjective valence ratings.

5.4 Results

5.4.1 Self-Assessment Manikin Ratings

As expected, arousal ratings differed between picture categories ($F(2, 100) = 188.4$, $p < .001$, $p = .88$) with aversive pictures being rated as more arousing compared to neutral ($p < .001$) as well as pleasant ($p < .001$) pictures. Pleasant pictures were also rated as more arousing than neutral pictures ($p < .001$). There was a significant interaction for group $\times$ category ($F(4, 100) = 4.25$, $p < .005$, $\varepsilon = .88$). Figure 2 shows the different patterns of arousal ratings for the distinct stimulus conditions for each participant group.

With respect to valence rating, the expected main effect for 'picture category' was found ($F(2, 92.9) = 1051$, $p < .001$, $\varepsilon = .81$). Overall, pleasant pictures were rated as more pleasant compared to neutral ($p < .001$) and unpleasant ($p < .001$) pictures. Neutral pictures were rated as more pleasant compared to unpleasant pictures ($p <$

.001). There was an additional main effect for group ($F(2, 57) = 8.4$, $p < .001$) which is illustrated in figure 2.

5.4.2 Minimum norm estimates (MNE) data

Permutation analyses revealed regions of interest (ROIs) with significant differences in pair-wise group comparisons. Figure 3 illustrates these group differences for the activation related to pleasant as well as to aversive visual stimuli. Both PTSD patients and Trauma Controls showed a reduced activation towards unpleasant pictures in central-left occipital brain regions (amplitude mean of dipole sites 93, 116, 117, 118) compared to the Unexposed Sample (patients vs. unexposed: $t = -2.91$, $p < .005$; trauma controls vs. unexposed: $t = -2.19$; $p < .05$). In the Trauma Control Group, a similar pattern was visible for the activation towards pleasant stimuli where, again, trauma controls showed a significant reduction in mean amplitude compared to the unexposed participants ($t = -2.19$; $p < .05$). In contrast, the difference between patients and unexposed subjects with respect to activation towards pleasant pictures did not yield statistical significance (see statistical maps in Fig. 3). However, patients differed significantly from trauma controls ($t = 3.69$; $p < .005$), showing a more pronounced activation towards pleasant pictures at occipital dipole site 116.

With respect to the difference in activation between unpleasant and neutral pictures, permutation tests revealed the superior parietal cortex (dipole 15) as a further ROI where PTSD patients showed an increased activation towards high arousing aversive stimuli compared to Trauma Controls ($t = 2.12$; $p < .05$). At this site, the elevated response towards unpleasant pictures for PTSD patients when compared to the Unexposed Group approached significance ($t = -1.91$; $p = .06$). To provide a better overview, figure 4 depicts mean difference values for activation towards pleasant and unpleasant slides at ROIs identified by the permutation tests (occipital brain regions and superior parietal site).

5.4.3 Correlations between clinical variables, subjective affective ratings, and activation in occipital and superior-parietal brain regions

With respect to affective ratings, no group showed a significant relationship between SAM arousal or valence rating differences and corresponding activation patterns at occipital or superior parietal regions (ROIs). As can be seen in table 3, activation towards unpleasant, neutral and pleasant pictures was also independent of clinical scores on the CAPS, the HDRS, and the SOMS-7 with respect to both regions of interests. A significant positive correlation was found between torture severity (the amount of torture events ever experienced) and SSVEF source amplitudes in response to unpleasant pictures over the superior parietal cortex (Rank correlation $r = .37$; $p < .05$). A graphical illustration of this relationship is presented in figure 5.

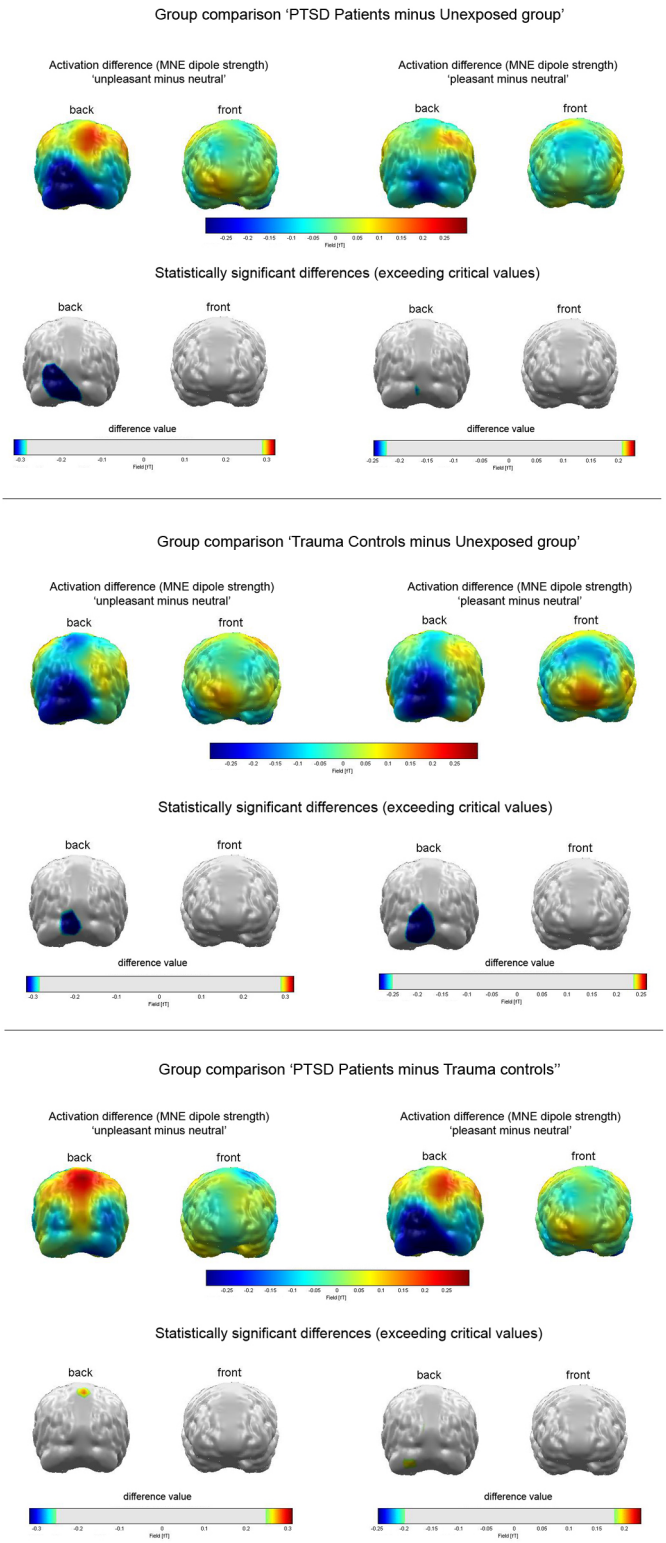

Figure 5.3: Brain maps showing significant group differences with respect to cortical source activation towards unpleasant (left) and pleasant (right) picture content. For each of the three group comparisons, the upper series of brain plots show overall activation differences. The lower row of each comparison depicts those cortical sources which indicate significant differences between groups as calculated in the permutation analysis.

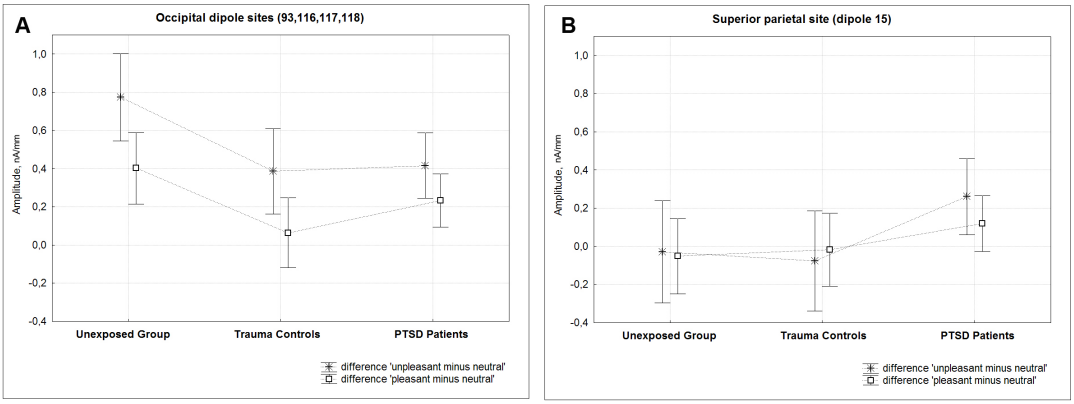

Figure 5.4: Groups mean activation (in nA/mm) towards high arousing unpleasant and pleasant slides at ROIs (A: Mean activation difference at four occipital dipole sites, B: Activation differences at superior parietal site). Error bars indicate 95% confidence intervals.

Table 5.3: Spearman rank correlations between trauma load and clinical variables and activation towards emotional pictures across all trauma-exposed participants, separately for each affective category

	Occipital activity (pleasant)	Occipital activity (neutral)	Occipital activity (unpleasant)	Superior parietal activity (pleasant)	Superior parietal activity (neutral)	Superior parietal activity (unpleasant)
Nr of traumatic events (CAPS)	-.16	-.16	-.19	-.10	-.14	.04
Nr of war events	.06	-.05	.06	.10	-0.02	-0.06
Nr of torture events	.12	.12	.15	.15	.29	.36 *
PTSD severity score (CAPS)	-0.08	-.07	-.08	-.15	-.19	-.08
Re-experiencing score	.04	.04	.02	-.19	-.24	.02
Avoidance score	-.20	-.20	-.21	-.12	-.17	-.21
Hyperarousal score	-.07	-.07	-.07	-.23	-.16	-.07
Depression Score (HDRS)	-.01	.01	.03	-.12	-.19	-.08
Nr of somatic complaints (SOMS-7)	-.13	-.11	-.06	-.10	-.17	-.10

Note: * indicate correlations significant on $p < .05$

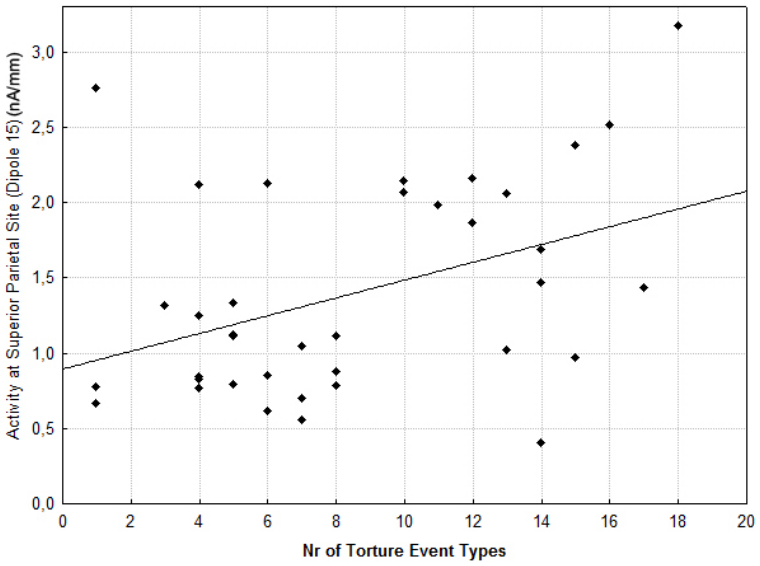

Figure 5.5: Scatterplot illustrating the relationship between the number of torture events and superior parietal activity (dipole 15) towards aversive slides (n = 37 participants with at least one torture experience are included)

The comparison between PTSD patients with dissociative symptoms and those without showed a significant difference ($t = -2.37$; $p < .05$) with respect to SSVEF source amplitudes in response to unpleasant pictures over the superior parietal cortex (dipole 15). PTSD patients with current dissociative symptoms showed a higher activity towards unpleasant slides (mean activity = .014 nA/mm) compared to PTSD patients without those specific features (mean activity = 0.48 nA/mm.

5.5 Discussion

The present findings point towards a deviant processing of aversive pictures and, to a smaller extent, of high arousing pleasant pictures in individuals traumatized by war and torture. Consistent with previous research, we found higher activation over occipital areas towards high-arousing pictures in healthy subjects. Studies examining ssVEF as well ssVEP changes as a function of emotional arousal have shown greater amplitudes in regions involving the occipital cortices and temporo-parietal cortices (A. Keil et al., 2003; Kemp et al., 2002; Moratti et al., 2004). These findings are typically discussed within the framework of selective attention, suggesting that more attentional resources are allocated to external stimuli according to their affective significance to enhance sensory processing of relevant information (Hillyard & Anllo-Vento, 1998; P. J. Lang

et al., 1997). In the present study, the preferential visual encoding of aversive stimuli was significantly reduced in the central-left occipital cortex in both PTSD patients and Trauma Controls. For PTSD patients, this hypoactivation in comparison to healthy controls was specific for aversive stimuli whereas the Trauma Control group showed similarly reduced steady-state responses in primary visual areas for pleasant pictures as well. The current finding of a decrease of the neurophysiological response towards aversive stimuli is in line with previous studies showing reduced ERP components to angry faces (Felmingham et al., 2003) and traumatic words (Kounios et al., 1997). In both of these studies, however, reduced event-related activity was found for aversive as well as for neutral stimuli indicating a generally reduced cortical activity in PTSD. Based on these findings, the authors suggested the presence of an adaptive sensory-gating mechanism in PTSD (Felmingham et al., 2003). In the present study, the assumption of a more general sensory-gating mechanism seems to be true for individuals who have experienced trauma without developing PTSD. The significant reduction of the activation towards both, pleasant and aversive high arousing pictures in the Trauma Control Group is in line with the assumption of a cortical inhibition mechanism in response to highly emotional cues that might represent a protective factor for the development of PTSD after trauma experiences.

In contrast to the Trauma Controls, PTSD patients showed a selective and more pronounced decrease of their ssVEFs in primary visual areas only in response to aversive pictures when compared to neutral ones. Applying Lang's theory of motivated attention (P. J. Lang et al., 1997, 1998b), one could assume that PTSD should be associated with an increase in sensory processing of aversive stimuli given their particular salience and motivational relevance. The cortical response pattern of PTSD patients in the present study, however, does not support this assumption but rather suggests that visual attention is lowered towards stimuli which are aversive and threat-related. A possible explanation could be that in PTSD patients, aversive pictures with such explicit contents as war and attack scenes are immediately categorized as a threat and do not require sustained visual processing to identify further emotionally relevant information. In this regard, studies using a rapid serial visual presentation method with healthy subjects have shown that affective processing of pictures occurs with great rapidity with high-arousing emotional slides activating occipito-parietal areas as early as 150 ms after stimulus onset (Junghöfer et al., 2001, 2006). In the future, similar studies should be carried out with PTSD patients in order to distinguish between rapidly occurring discriminative cortical mechanisms and sustained attentional processing of emotional pictures. In line with this thinking, a recent ERP study showed an enhanced initial threat evaluation but an attenuation of later cognitive processing of fearful faces in individuals with high anxiety compared to low-anxiety subjects (Holmes et al., 2008).

In all subject groups, ssVEF amplitudes towards unpleasant or pleasant pictures at occipital sites were not significantly related to any clinical score (CAPS, HDRS or SOMS-7) or to trauma severity. Also the subjective evaluation of pictures did not yield

a similar pattern when compared with brain responses. To our knowledge, no analogous data with PTSD patients have been published so far, but studies with other clinical populations have shown that physiological reactivity during emotion processing and subjective evaluation of the stimuli can dissociate (Moratti et al., 2008; Holmes et al., 2008). The finding, that both, PTSD patients and Trauma Controls rated pleasant pictures as less arousing compared with the Unexposed Group could be related to the higher depression scores in the two trauma-exposed samples. In fact, previous studies on depressive patients have shown diminished emotional responses to pleasant stimuli (Sloan, Strauss, & Wisner, 2001; Sloan, Strauss, Quirk, & Sajatovic, 1997). The finding of the present study that PTSD patients rated all pictures as less pleasant, might therefore reflect the fact that the majority of the patients had co-morbid Major Depression. In addition to the activation pattern in occipital brain areas, permutation analyses yielded a PTSD specific response towards aversive stimuli in the superior parietal cortex (SPC). At this site, we found a significantly augmented steady-state response towards unpleasant pictures in PTSD patients compared to Trauma Controls and, on a statistical trend level, to the Unexposed Group. In humans, the SPC is known to play a role in spatial information processing (Corbetta, Shulman, Miezin, & Petersen, 1995; Han & Jiang, 2004) and contributes to top-down attentional processes on episodic memory (Cabeza, 2008). Results from a study measuring regional cerebral blood flow in PTSD patients while performing a visuoverbal task show a higher activation of the superior parietal lobule in patients compared to healthy subjects (Clark et al., 2003). The authors suggested an increased reliance of working memory function on the visuospatial coding of information in PTSD patients.

Intriguing findings about a specific involvement of the SPC in dissociative symptoms in traumatized individuals emerged from neuroimaging studies with PTSD subjects (Lanius et al., 2005, 2002) and patients with Borderline-Personality Disorder (BPD) who had been exposed to childhood abuse (Irle, Lange, Weniger, & Sachsse, 2007). Lanius and co-workers found increased activity of the SPC in PTSD patients with trauma-related dissociative states during script-driven imagery. The enhanced SPC activity did differentiate PTSD patients with a dissociative response to the traumatic script-driven imagery and those who had a flashback/reliving response to the script (Lanius et al., 2005). In line with these findings, in the present study, PTSD patients with current dissociative symptoms showed a higher superior parietal activation towards aversive stimuli compared to non-dissociative PTSD patients. In addition, we found a positive correlation between the amount of torture events ever experienced by trauma-exposed subjects and steady-state amplitudes in the SPC in response to aversive pictures. A possible explanation for this finding might be that torture experiences represent a massive and often chronic form of traumatization that typically does not only lead to PTSD but to a variety of other clinical disorders including dissociative symptoms (Basoglu, Jaranson, Mollica, & Kastrup, 2001; Campbell, 2007; Carlson & Rosser-Hogan, 1994). Emphasizing the important role of dissociative features in survivors of torture, a previ-

ous study examining generators of cortical slow waves reported brain abnormalities in torture survivors with PTSD that were associated to the amount of dissociative experiences (Ray et al., 2006). Given that in the present study, no other clinical score was significantly related to SPC hyperactivation towards aversive stimuli our data suggest a specific involvement of the superior parietal lobe in the processing of aversive cues which is mediated by the amount of torture experiences and the presence of dissociative symptoms in PTSD individuals. However, results of the correlational analyses should be interpreted with caution given that we had no a-priori hypotheses for the relationship between clinical data and cortical activation patterns and did not correct for multiple comparisons.

Another limitation of the present study is that group differences cannot be solely attributed to PTSD status because there were substantial differences between groups in particular with respect to comorbid depression as well as slight differences regarding the use of antidepressants. However, this problem is inherent in most PTSD research because PTSD is commonly associated with other disorders. Also, a recent MEG study with medicated depressive patients has reported a very different pattern of abnormalities during processing of high arousing stimuli (Moratti et al., 2008) compared to the present outcome for PTSD patients, supporting the assumption that a possible confounding effect of depressive symptoms cannot explain group differences found in the present work. As a methodological constraint, the present study employed a homogenous sphere as a head model for the MNE. Thus, cortical areas involved in generation of the signal were inferred from localizations on a shell. Still, we consider this approach more accurate than simply inferring activation of cortical areas from sensor topographies. Ideally, future studies should utilize realistic head models derived from subjects' individual structural MRIs to obtain more exact identification of brain regions.

Based on the results of the present study, we cannot determine whether the occipital hypoactivation in PTSD patients reflects a specific response towards trauma-related stimuli or towards high arousing aversive pictures in general. As the majority of pictures showed human attacks, war scenes or injuries, most of them might have triggered memories related to the individual traumatic experiences. It remains a challenging task for future investigations to disentangle these responses. Ideally, studies should be carried out with a wide range of unpleasant pictures including trauma-related and non-trauma-related slides being shown to patients affected by a very specific trauma type (e.g., only car accident victims).

In conclusion, we found that the response pattern of the occipital cortex as well as the superior parietal cortex in response to aversive stimuli discriminates between non-traumatized subjects as well as victims of war and torture with and without PTSD. The occipital hypoactivation of the trauma survivors is independent of psychopathology and might represent an adaptive adjustment of the brain to living in a threatening environment. It can be speculated that this form of inner shut-down of the visual system is the cost for the rapid allocation of resources towards a defensive reaction immediately after

the classification of a cue as threatening. However, it seems that the human cortical attention system can be shaped by life experiences in an adaptive or a pathological way, as we found an opposite response pattern of the superior parietal cortex for trauma survivors with and without PTSD. The pathological way of cortical attention allocation after aversive stimuli involves hyperactivation of the SPC and is related to more traumatic events, more PTSD symptoms and the presence of dissociative symptoms. Future studies could try to disentangle the predictors of the pathological attention pathway and try to change this mechanism through behavioral training.

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6 Narrative Exposure Therapy for PTSD increases activity in cortical regions associated with top-down processing of aversive stimuli – evidence from a randomized controlled treatment trial

6.1 Abstract

Context Posttraumatic Stress Disorder (PTSD) is associated with altered processing of threatening stimuli. It remains unclear whether this functional abnormality can be changed by psychotherapy.

Objective The present randomized controlled treatment trial examined whether narrative exposure therapy (NET) causes changes in affective stimulus processing in patients with severe and chronic PTSD.

Design A randomized controlled comparison of a NET and a waitlist control (WLC) condition. At pre-test and at four-months follow-up, the diagnostics included the assessment of clinical variables as well as of neuromagnetic oscillatory brain activity (steady-state visual evoked fields, ssVEF) resulting from exposure to aversive pictures compared to neutral pictures.

Setting A University outpatient clinic.

Participants 34 refugees (mean age: 33.5, SD = 9.93, 15 female) with war and torture experiences diagnosed with PTSD. Complete data was available for 19 subjects.

Intervention Treatment consisted of 12 sessions of NET. NET and WLC participants did not significantly differ in symptom severity, age, sex, and ethnicity.

Main Outcome Measures Neuromagnetic cortical activity during affective picture processing determined by minimum norm source localization of ssVEFs prior to and after treatment. Changes in clinical outcomes (PTSD and depressive symptom severity) were assessed by standardized clinical interviews before and after treatment.

Results PTSD as well as depressive symptom severity scores declined in the NET group, whereas symptoms persisted in the WLC group (Time × Group interactions of PTSD and depressive symptom severity: $p < .005$). Parietal and occipital activity related to threatening compared to neutral pictures increased significantly after therapy ($p < .05$ for permutation statistics) in the NET group only.

Conclusions Our results indicate that Narrative Exposure Therapy causes an increase of activity associated with cortical top-down regulation of attention towards aversive pictures. The increase of attention allocation to potential threat cues might allow treated patients to re-appraise the actual danger of the current situation, thereby, reduce PTSD symptoms.

6.2 Introduction

A cardinal characteristic of anxiety disorders is the so-called attentional bias (Fox, Russo, & Dutton, 2002; Buckley et al., 2000; A. Ehlers & Clark, 2000), which refers to alterations of attentional processes in response to emotional, especially threat-related, stimuli. These deviations of stimulus processing probably reflect changes in the functioning of subcortical and cortical fear processing structures, which include the amygdala as well as the prefrontal cortex (Davis & Whalen, 2001; B. J. Liddell et al., 2005). The attentional bias of subjects with trait anxiety (Koster et al., 2005; Mogg et al., 2004) as well as anxiety disorders (Chen, Ehlers, Clark, & Mansell, 2002; Amir, Foa, & Coles, 1998) including PTSD (Adenauer et al., submitted) has recently been described as a 'vigilance-avoidance reaction'. This model can reconcile the apparently contradicting findings of an increased allocation of attention resources towards aversive stimuli in PTSD that has been found in some studies (McNally et al., 2000; R. A. Bryant & Harvey, 1997), as well as an attentional bias away from threat reported elsewhere (Pine et al., 2005; Catani, Adenauer, et al., 2009). A recent magnetencephalographic study indicated that the vigilance-avoidance pattern in PTSD consists of two distinct processes that are temporally and spatially dissociated (Adenauer et al., submitted). PTSD patients showed a hyper-reaction to threatening stimuli in the ventrolateral prefrontal cortex as early as 130 ms after stimulus onset, which was followed by an attentional avoidance reaction in occipital regions starting at 200 ms after stimulus onset. Catani, Adenauer, et al. (2009) found that the avoidant reaction to aversive pictures in PTSD, indicated by a reduced activity in the left occipital lobe, remained stable for at least the

first four seconds after stimulus onset. This reduced activity in brain regions that are associated with elaborate visual processing, was interpreted as disengagement from a detailed visual stimulus exploration (Catani, Adenauer, et al., 2009). Confronted with potential threats, subjects with anxiety disorders seem to focus on the initiation of a rapid flight reaction rather than concentrating on the attentive evaluation of the threat cue (Adenauer, Catani, Keil, Aichinger, & Neuner, Epub 2009). As it is plausible to assume that such a mechanism can contribute to the maintenance of anxiety symptoms, it could be a promising target for therapeutic interventions. However, the early onset of both the transient vigilant response as well as the prolonged avoidant reaction indicates that both reactions are automatic, stimulus driven bottom-up processes, which cannot be consciously altered by verbal instructions.

Accumulating evidence from treatment trials demonstrates that PTSD can be effectively treated with psychotherapy. A large number of randomized controlled trials have shown that variants of trauma-focused cognitive behavioral therapy (CBT) are the most successful interventions for the treatment of PTSD (Foa, Keane, & Friedman, 2000; Bisson et al., 2007). The active mechanism of therapeutic change is thought to be the imaginal exposure to the episodic memory of the traumatic event. In this procedure, the patient is instructed to overcome avoidant strategies and to narrate the traumatic experience in detail. The repeated re-experiencing is thought to reconstruct the distorted autobiographic memory of the trauma (Foa & Rothbaum, 1998) and to change pathological mechanisms of fear processing.

Little is known, however, about the neurobiological foundations of psychotherapy for PTSD. Three uncontrolled small-scale studies have examined neuronal changes over the course of psychotherapy. While no changes were found on a structural level (Lindauer et al., 2005; Bossini, Fagiolini, & Castrogiovanni, 2007), Felmingham et al. (2007) reported a change of activity of basic fear processing mechanisms in eight subjects who underwent CBT for PTSD. In particular, after therapy, amygdala activity reduced while the activity of the anterior cingulated cortex, which is associated with a top-down influence on fear processing, increased. As this study lacked a control group however, brain changes could not be causally linked to psychotherapy. To our knowledge, there are only two randomized trials that assessed functional changes of neural correlates in PTSD. These studies reported a decrease of cortical activity in the right anterior hemisphere during exposure to trauma-related pictures (Rabe, Zoellner, Beauducel, Maercker, & Karl, 2007) and the right middle frontal gyrus during trauma script-driven imagery (Lindauer et al., 2007).

Although the primary intention of CBT is to target trauma memories rather than to change attentional processes, the interaction of episodic memory retrieval and attention supports the assumption that trauma focused CBT alters both, memory as well as attention processes. In the present randomized controlled treatment trial, we wanted to investigate the influence of trauma-focused therapy on early attentional processing of aversive pictures. We compared the effects of trauma-focused CBT with a waitlist

control group in a population of severely traumatized victims of war and torture. In both groups, we assessed neurophysiological indicators of attention to threat cues before and after treatment or the corresponding waiting time. We used Narrative Exposure Therapy (NET) as a variant of trauma-focused CBT. NET is a manualized short-term approach that has been adapted to meet the needs of traumatized survivors of war and torture (Schauer, Neuner, & Elbert, 2005). NET has been shown to be effective in the reduction of PTSD symptoms in various randomized controlled trials (Catani, Kohiladevy, et al., 2009; Neuner et al., Epub 2009; Schaal, Elbert, & Neuner, 2009; Neuner, Schauer, Klaschik, Karunakara, & Elbert, 2004). The advantage of NET is that rather than combining various techniques such as cognitive methods and skills training, this treatment focuses exclusively on the reconstruction of episodic trauma memory by a detailed and emotional narration of the biography, with particular emphasis on the traumatic events. Therefore, potential effects can be attributed to a specific intervention rather than to a mixture of various therapeutic methods.

We applied magnetencephalography (MEG) to measure steady-state visual evoked fields (ssVEF) as an indicator of attention processes. Here, we were interested in the processing pattern of threatening cues, which consisted mainly of pictures with trauma-related (war and attack scenes) or generally aversive (mutilations) stimuli. The ssVEF represents an ongoing cortical oscillatory neuromagnetic response elicited by a repetitive visual stimulus that is presented at a certain frequency (e.g., 10 Hz) having the same fundamental frequency as the driving stimulus (Regan, 1989). One major advantage of the ssVEF technique is that a high signal-noise-ratio can be achieved even with a limited number of trials (J. Keil, Adenauer, Catani, & Neuner, 2009). This technique has proven its efficiency in several studies investigating higher order attentional mechanisms during the processing of emotional stimuli in healthy participants (J. Keil et al., 2009; A. Keil et al., 2003; Moratti et al., 2004), and psychiatric patients (Moratti et al., 2008; Catani, Adenauer, et al., 2009).

We expected that NET would reduce attentional disengagement towards aversive stimuli. Therefore, we expected a relative increase of activity towards threat-related pictures in brain regions associated with elaborate visual processing and attention.

6.3 Methods

6.3.1 Participants

The study was carried out at the Psychological Research and Outpatient Clinic for Refugees at the University of Konstanz. Participants were refugees and asylum seekers who were referred for diagnostic examination or treatment by general practitioners, aid organizations, lawyers, or judges. Inclusion criteria were a history of organized violence or persecution and current PTSD diagnosis according to DSM-IV. Exclusion criteria were current psychosis, substance or alcohol dependence. 34 participants who fulfilled

inclusion criteria (see flowchart figure 1) were randomly assigned to either a treatment (NET) group (n = 16) or a Waitlist Control (WLC) group (n = 18). There were no significant differences in any of the demographic or clinical characteristics following randomization. Participants who completed therapy as well as the MEG examination at posttests and produced MEG data sets (pre and post) that could be included in the final analysis were defined as 'study completers' (SC). Among the study completers, there was no significant difference in any demographical or clinical variables between the two treatment groups except in the CAPS score.

6.3.2 Procedure

6.3.3 Clinical Assessement

The Ethical Committee of the University of Konstanz approved the study protocol and all participants gave written informed consent. The initial assessment consisted of an extensive structured clinical interview and a MEG examination. Clinical psychologists with expertise in the examination of refugees with PTSD carried out the diagnostic interviews with the help of interpreters. MEG recordings took place one week after clinical examination to avoid any possible influences of the diagnostic interview. Participants that fulfilled the inclusion criteria were randomized into the two groups using a computer-generated list of random numbers. Treatment consisted of 12 therapy sessions on a weekly or biweekly basis. On average, treatment sessions lasted 108 (SD = 17.0) minutes. Treatment adherence was monitored by means of regular supervision. Furthermore, all testimonies gained in NET treatment (biographical narrations usually exceeding 8000 words) were checked for indicators of vividness and consistency to ensure proper application of NET. No major deviations from treatment protocol were detected.

Posttests with the NET patients were scheduled 4 months after the end of therapy. For the participants in the WLC group, the time spans between pre- and posttests were individually matched with the NET group. Posttests included the same instruments as used in the pretest and were carried out by interviewers who were blind to the individual participant's treatment condition. As part of the posttest, the same MEG examination as in the initial assessment was conducted with each patient.

6.3.4 Clinical Assessment

The clinical assessment included a detailed structured interview regarding demographic data, traumatic experiences and psychiatric diagnoses. For the examination of traumatic life events, we used the vivo Checklist of War, Detention, and Torture Events and the Event Checklist of the Clinician Administered PTSD Scale, CAPS (Blake et al., 1995). Standardized clinical instruments were used for the determination of DSM-IV diagnoses: The CAPS for diagnosis and quantification of PTSD, the MINI International

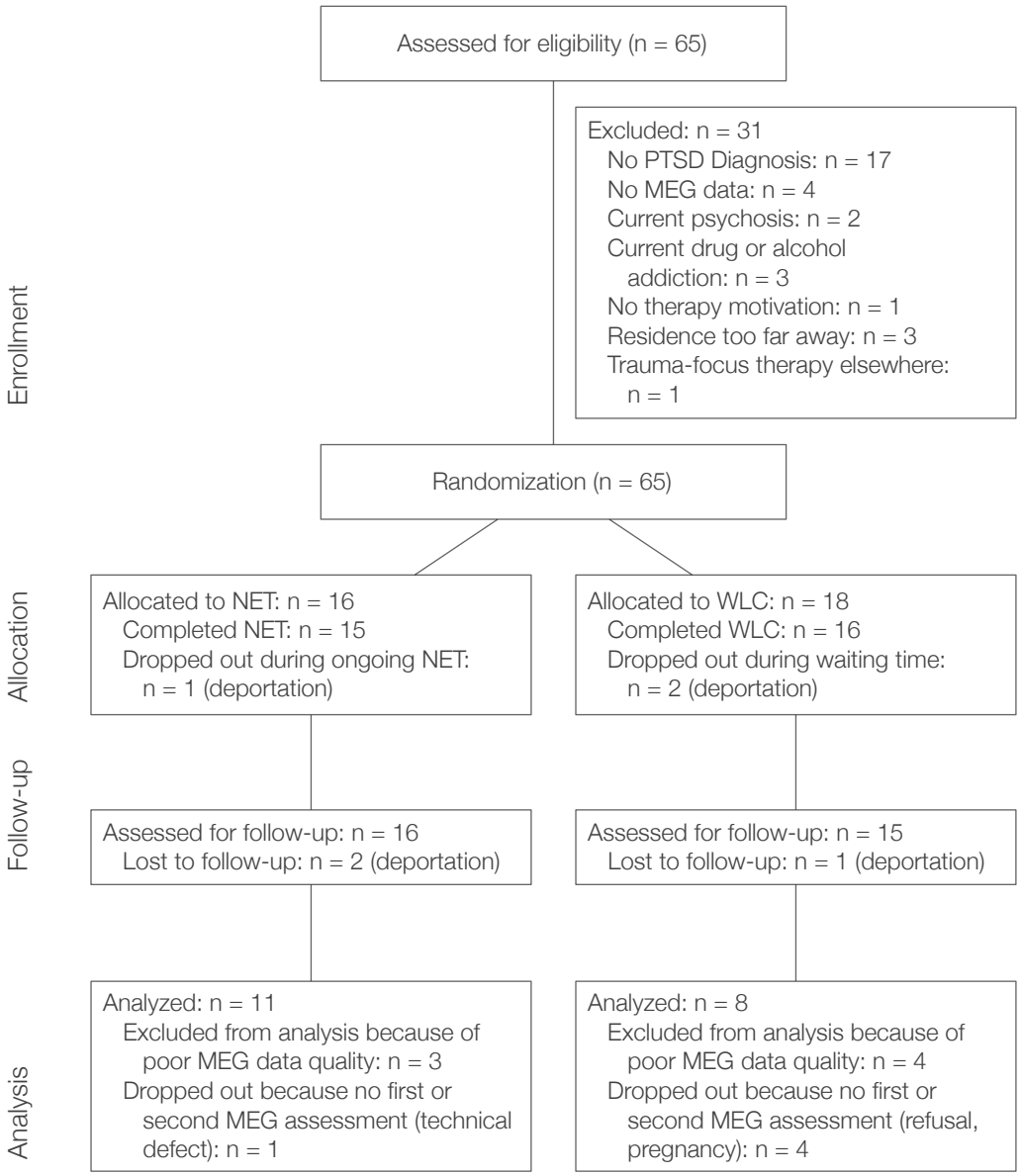

Figure 6.1: Flowchart of study participants

Table 6.1: Pre-treatment demographic and clinical characteristic of study participants. Study Completers were called only those participants, who completed therapy and produced MEG data sets (pre and post) of good quality that could be included in the final analysis.

		Intention to Treat			Study Completer		
		NET (n=16)	WLC (n=18)	*p*	NET (n=11)	WLC (n=8)	*p*
Demographic Data							
Sex				0.97			0.31
female	*N (%)*	7 (43.8)	8 (44.4)		3 (27.3)	4 (50.0)	
male	*N (%)*	9 (56.3)	10 (55.6)		8 (72.7)	4 (50.0)	
Age	*M (SD)*	30.3 (9.2)	36.4 (9.9)	0.09	28.6 (8.6)	33.6 (9.8)	0.25
Education (ys school)	*M (SD)*	8.7 (3.3)	7.8 (3.3)	0.51	8.9 (3.4)	7.9 (2.7)	0.51
Regions of Origin				0.15			0.65
Middle East	*N (%)*	8 (50.0)	11 (61.1)		6 (54.6)	4 (50.0)	
Central East	*N (%)*	2 (12.5)	1 (5.6)		1 (9.1)	1 (12.5)	
The Balkans	*N (%)*	-	3 (16.7)		-	1 (12.5)	
Africa	*N (%)*	6 (37.5)	2 (11.1)		4 (36.4)	2 (25.0)	
Asylum Status (insecure)	*N (%)*	14 (87.5)	18 (100.0)	0.12	9 (81.8)	8 (100.0)	0.20
Clinical Data							
Events							
CAPS Event-Types	*M (SD)*	7.4 (2.3)	6.6 (2.0)	0.31	7.0 (2.3)	6.5 (2.1)	0.71
Nr War&Torture-Types	*M (SD)*	11.3 (5.6)	9.4 (4.7)	0.29	11.4 (6.7)	7.6 (4.9)	0.16
Clinical Symptoms							
CAPS Score	*M (SD)*	89.5 (14.7)	80.1 (16.5)	0.16	88.0 (12.5)	72.0 (13.8)	0.04
HDRS	*M (SD)*	27.3 (8.1)	27.3 (6.9)	0.74	25.8 (7.9)	27.4 (5.6)	0.77

Note: For pair-wise group comparisons of continuous variables, Mann-Whitney U Tests were used; differences of categorical variables were evaluated by applying χ^2-Tests for independence.

Neuropsychiatric Interviews, M.I.N.I. (Sheehan et al., 1998) for comorbid DSM-IV axis one disorders, and the Hamilton Depression Rating Scale, HDRS (J. B. Williams, 1988) for determining the severity of depressive symptoms.

6.3.5 Neuromagnetic examination

We applied magnetoencephalography to measure steady-state visual evoked fields during the presentation of standardized affective pictures varying with respect to emotional content. Full details of the neuromagnetic examination procedure including stimulation, procedure, data preprocessing and analysis have been provided previously (Catani, Adenauer, et al., 2009; J. Keil et al., 2009) and are described only briefly here.

6.3.6 Stimuli

Seventy-five colored pictures were chosen on the basis of their normative ratings from the International Affective Pictures Rating (IAPS) (P. Lang, Bradley, & Cuthbert, 1997). Of these, 25 pictures presented threat-relevant events (e.g., mutilations, assaults, weapons), 25 pleasant events (e.g., sports, erotic couples, children) and 25 neutral events (e.g., neutral faces, household objects). Pictures were presented with a video projector on a white plastic screen attached to the ceiling of the shielded MEG chamber. In each trial, one picture was presented in a flickering mode of 10 Hz for 4 seconds with an inter-trial interval that varied randomly between 6 to 8 s.

After the initial MEG recording, subjects rated each of the 75 affective pictures regarding for emotional valence and arousal using the Self-Assessment Manikin (SAM) scale. Two participants of the WLC group did not complete SAM ratings. Arousal ratings differed between picture categories ($F(2, 28) = 90.6$, $p < .001$, $\varepsilon = .80$) with aversive pictures being rated as more arousing compared to neutral as well as pleasant ($p < .001$) pictures. There was no significant difference in the arousal rating between pleasant and neutral pictures.

Pictures differed significantly with respect to patients' valence ratings $F(2, 28) = 233.03$, $p < .001$, $\varepsilon = .73$). Overall, pleasant pictures were rated as most pleasant, followed by neutral and finally by aversive pictures (all comparisons $p < .001$). There were no statistical differences between the treatment groups with respect to their arousal or valence ratings.

6.3.7 MEG Recording and Data Processing

MEG was recorded continuously and digitized at a rate of 678.17 Hz using a 148-channel whole head magnetometer (MAGNES^{TM} 2500 WH, 4D Neuroimage, San Diego, USA) and an online band-pass filter of 0.1–200 Hz. Cardiac and eye artifacts were recorded with a SynAmps amplifier (Neuroscan^{TM}) and corrected offline using procedures included in the MEG acquisition software package (Whole Head system software, version

1.2.5; 4D Neuroimaging) as well as algorithms implemented in BESA™ software. In order to determine the position of the head in the MEG-dewar for source localization, individual head shapes and reference points were digitized before the recording session. Offline, MEG data were visually inspected and corrected for movement, cardiac, and eye artifacts as well as for global noise. MEG data were digitally band-pass filtered between 1 Hz and 25 Hz (slopes: 6 and 24 dB/octave, respectively). Finally, trials were baseline corrected (500 ms baseline) and averaged over picture category (pleasant, neutral and aversive). For each category average, a moving window averaging procedure was applied (Moratti et al., 2004; A. Keil et al., 2008). To avoid contamination of results with the event related early activity, the initial 400 ms of the picture presentation interval were excluded. A 400 ms window containing four cycles of the 10 Hz flickering stimuli was shifted in steps of 100 ms (one cycle) across the epoch, and the magnetic field data within the shifting windows in the time domain were further averaged. As a result, we obtained for each category, subject, and MEG channel a 400 ms segment of four 10 Hz cycles reflecting an average across 32 sliding windows. These four cycles were submitted to fast Fourier transform (FFT) technique and the extracted real and imaginary parts of the 10 Hz Fourier coefficients were used for source localization.

Using the Matlab-based software EMEGS© (Junghöfer & Peyk, 2004), the distribution of likely generators of the neuromagnetic activity was estimated by calculating L2 minimum norm solutions based on a spherical one shell (6 cm radius) head model with 197 evenly distributed dipolar sources (Hauk, 2004).

6.3.8 Treatment

Clinical psychologists of the University of Konstanz with expertise in PTSD and NET carried out treatment according to the manual (Schauer et al., 2005) with the help of a translator, if necessary. During the therapy sessions, the patient, assisted by the therapist, constructs a detailed chronological account of his or her own biography. Particular attention is given to traumatic experiences, often events linked to violence and war situations. The autobiography is recorded by the therapist in written form and is corrected and elaborated on each subsequent reading. The therapist writes down the biography and reads it out at the beginning of each following session for completion and correction. The aim of the therapy is the reorganization of the generally fragmented report of traumatic experiences into a coherent narrative. During the confrontation with the aversive life events, the therapist asks for current and past emotional, physiological, cognitive, and behavioral reactions, and probes for respective observations. While narrating, the patient is encouraged to relive these emotions. The exposure to the traumatic experience is not terminated, until the related fear reaction, presented and reported by the patient, shows a significant diminution. During the last session, the participant receives the written report of his biography (Schauer et al., 2005). In order to meet the needs of patients with insecure asylum status, the last two NET

sessions were kept flexible to allow patients and therapists to discuss issues related to the current situation.

6.3.9 Statistical Analysis of Demographic and Clinical Data

Baseline characteristics of the groups were compared to examine the effects of randomization using the Mann–Whitney U test for continuous variables and the Chi-Square test for dichotomous variables. As this study focuses on brain changes through psychotherapy rather than examining the clinical efficacy of the treatment, we restricted all analyses on the sample of study completers. Changes in clinical symptoms were evaluated using repeated-measures ANOVA with Treatment Condition (NET and WLC) as between-factor and Time (pretest and posttest) as within-factor. Greenhouse-Geisser's correction of the degrees of freedom was used where appropriate. The associated epsilon and adjusted p-values are reported. Statistically significant interactions were investigated further by using Tukey's HSD test for post-hoc evaluation of unequal sample sizes. Moreover, clinical significance was estimated by calculating within-treatment effect sizes (Cohen's d) for PTSD (CAPS score) and depressive symptoms (HDRS score).

6.4 Analysis of MEG Data

For MEG data analysis, brain maps consisting of the MNE source strengths at 197 dipoles represented the cortical activity induced by the stimulation. The dependent variable in the analysis relates to the cortical activity induced by threatening stimuli. To control for different levels of overall stimulus-driven activity, we subtracted each subject's average activity related to neutral pictures from the average activity in response to threatening pictures ('aversive minus neutral' difference). The resulting individual condition contrast maps were averaged separately for the NET and the WLC groups. For simplicity reasons, we refer to the resulting contrast maps as Threat effects. As an indicator of the changes induced by treatment group (NET) and waiting time (WLC), we calculated the differences of the Threat effects between pre- and post test for each group. These contrast maps were defined as Time effects. Finally, the Time $\times$ Treatment interaction was determined as the contrast map that resulted from the group difference (NET minus WLC) within the Time effects.

The statistical analysis of the MEG data was carried out with permutation statistics rather than t-tests or ANOVAs for several reasons. First of all, due to the small sample size and the skewed distribution of the MEG data the prerequisites of parametric statistics were not fulfilled. In contrast, the permutation test does not require any a priori assumptions about the distribution of data, as it generates a representative subset of a sufficiently large number of permutations of the data to represent the data distribution (Ludbrook & Dudley, 1998; Karniski et al., 1994). Secondly, the permutation test avoids the danger of alpha inflation in the comparison of brain maps without

the necessity to pre-define regions of interest. The appropriateness of this procedure for analyzing visual-evoked steady-state responses has been demonstrated in previous studies (J. Keil et al., 2009; Moratti et al., 2008; Catani, Adenauer, et al., 2009). Permutation tests were calculated as follows. For each pair-wise comparison, we determined cut-off values for significant differences of the maps at single dipole locations based on 1000 draws. For each draw, the individuals' condition contrast maps were randomly exchanged between groups (NET vs. WLC) and between time points (pre vs. post) to generate data for a random composition with respect to group and time. The maximum as well as the minimum differences at all dipole locations obtained from each draw entered the distributions of 1000 maximum and minimum difference values. The upper and the lower critical values were determined as the 25th lowest and highest values in this distribution ($p < .05$). Values indicating a significant difference (smaller than the lower and higher than the upper critical values) were plotted onto the MNI brain. For illustrative purposes only, we calculated t-tests for each pair-wise comparison.

6.5 Results

6.5.1 Clinical Data

Within the study completer sample, the Time $\times$ Treatment interaction revealed a significant difference of the development of both groups with respect to the CAPS score ($F(1, 17) = 34.99$, $p < .001$). In patients treated with NET, PTSD symptom severity significantly reduced at the 4-months posttest ($p < .001$) while the WLC group showed no significant improvement ($p = .11$). Moreover, an interaction effect for Time $\times$ Treatment was found for the Hamilton Depression Rating Scale ($F(1, 17) = 13.2$, $p < .005$). The NET group reported significantly less depressive symptom severity at posttest ($p < .001$) while depressive symptoms stayed unchanged in the WLC group ($p = .99$). Table 2 provides an overview on PTSD and Depression severity scores at pre- and posttest for each treatment group. Four months after therapy, almost half of the NET group (45.5%) did not fulfill the diagnostic criteria of PTSD anymore. All patients of the WLC condition still met diagnosis of PTSD after matched waiting periods. In the NET group, within-treatment effect sizes were $d = 2.21$ for the CAPS score and $d = 1.56$ for the HDRS score. In the WLC condition, effect sizes were $d = -0.97$ for the CAPS score and $d = -0.07$ for the HDRS score.

6.5.2 Minimum norm estimates (MNE)

At pretest, cortical source activation towards aversive pictures did not differ between the two treatment groups at any dipole location (see figure 2).

Permutation statistics calculated within each group resulted in a significant Time effect, only in the NET group. Patients treated with NET showed an increase of cortical

Table 6.2: Changes of PTSD and depressive symptoms through therapy.

		pre-test	post-test	*p*
PTSD symptoms				
CAPS score				
NET (n=11)	*M (SD)*	88.0 (12.5)	52.8 (18.8)	< .001
WLC (n=8)	*M (SD)*	72.0 (13.8)	87.9 (18.5)	n.s.
Depressive symptoms				
HDRS score				
NET (n=11)	*M (SD)*	25.8 (7.9)	14.9 (5.5)	< .001
WLC (n=8)	*M (SD)*	27.4 (5.6)	27.9 (7.4)	n.s.

Note: Change scores were analyzed with repeated measures ANOVAs.

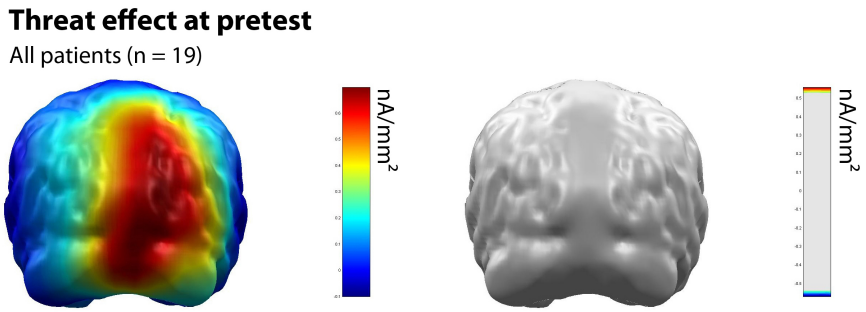

Figure 6.2: Threat effect (source activation difference 'aversive minus neutral') for all patients at pretest. Color bar indicates dipole source strength (left). Permutation statistics revealed no significant difference between the NET and the WLC group (right).

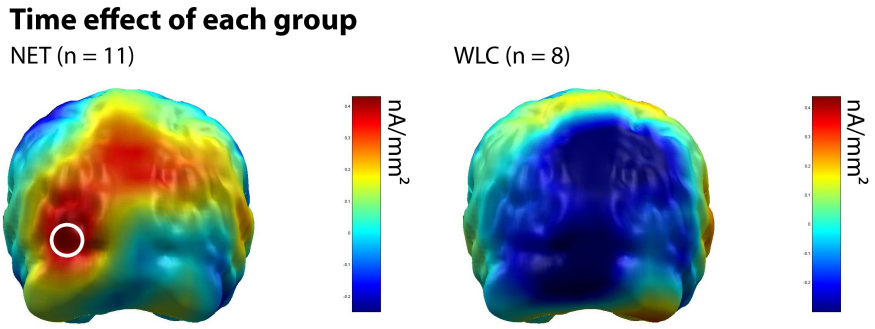

Figure 6.3: Time related changes in cortical source activation (pre minus post). The circle marks significant differences as indicated by permutation statistics. Color bar indicates dipole source strength.

activity towards threatening stimuli at left occipital brain regions (dipoles 91 and 92) from pre- to posttest. This effect was confirmed by paired t-tests (NET: $t = -3.35$, $p = .007$). In the WLC group, cortical source activity did not differ in this cortical region between pretest and posttest ($t = 0.58$, $p = .58$). Figure 3 shows Time effects for each group separately.

With respect to the Time $\times$ Treatment interaction, the permutation test revealed a significant effect in the superior parietal cortex (dipoles 47 and 48), which is shown in figure 4. To illustrate the effects, unpaired t-tests were calculated within this region of interest for both recording sessions (pretest: $t = 0.31$, $p = .76$, posttest: $t = 2.58$, $p = .02$). Means of the Time effect in occipital regions and the Threat effect in parietal regions are shown separately for NET and WLC patients in figure 5.

6.6 Discussion

The present randomized controlled treatment trial shows that Narrative Exposure Therapy was effective for the treatment of PTSD symptoms and comorbid depression in traumatized survivors of war and torture. Furthermore, NET changed neural correlates of the processing of aversive stimuli. Specifically, treatment increased the activity of the superior parietal cortex. In addition, patients treated with NET showed an augmentation in occipital activation. These results point at potential neuronal mechanisms underlying effective psychotherapy for PTSD.

After therapy, PTSD patients showed a significant increase in parietal activity towards aversive pictures compared to the Waitlist Controls. Even though some studies point to the involvement of the parietal cortex in PTSD (Clark et al., 2003; Lanius et al., 2005, 2002), until now, no consistent theory exists about its specific role in this dis-

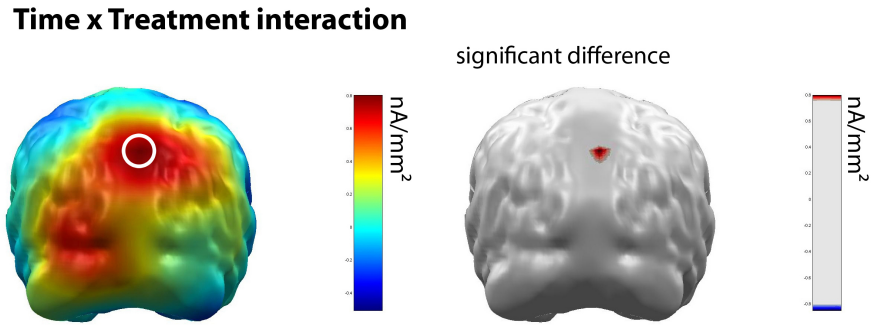

Figure 6.4: Group differences in pre to post changes in source activation of the Threat effect. The circle marks significant differences as indicated by permutation statistics. Color bar indicates dipole source strength (left). Significant differences of source activation as calculated in the permutation analysis. Color marks significant effects (right).

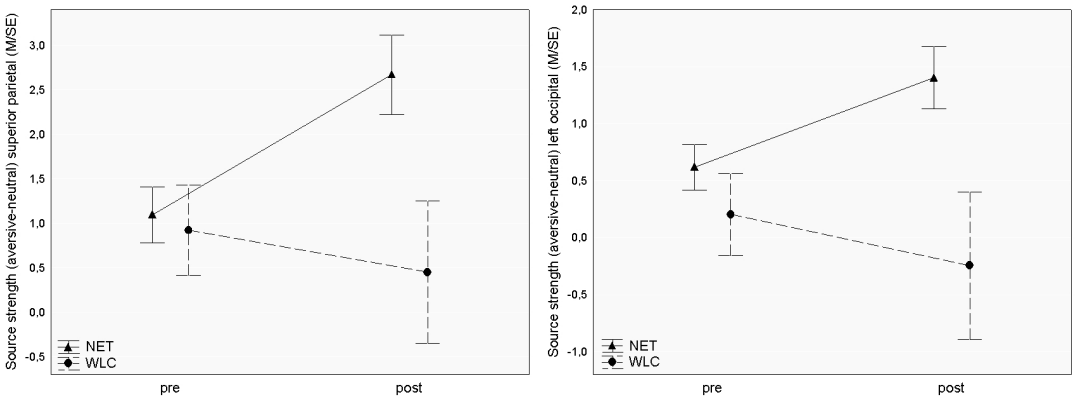

Figure 6.5: Means of dipole source strength at pretest and posttest in the superior parietal ROI (left) and the occipital ROI (right) for the NET and the WLC group, respectively.

order. The parietal cortex is traditionally associated with attentional processes (Posner & Petersen, 1990). Recent studies, however, showed that the parietal cortex is also relevant in episodic memory retrieval (Cabeza, 2008; Berryhill, Phuong, Picasso, Cabeza, & Olson, 2007). Recently, Cabeza, Ciaramelli, Olson, and Moscovitch (2008) formulated a theory that connects attentional and episodic memory processes. According to this theory, goal-directed memory retrieval can be regarded as an effortful process that involves voluntary top-down attention towards memory content. These goal-directed attentional processes are proposed to be driven by parietal structures including the superior parietal cortex. This finding is important to interpret the role of the parietal cortex in PTSD considering the general assumption of a deficit in top-down regulation of fear in PTSD (Shin et al., 2006), which may be modified by exposure therapy (Felmingham et al., 2007). More specifically, it can be speculated that the increase of parietal activity in treated patients in the present study, represents voluntary top-down episodic memory search that was trained through the procedure of NET, which requires the detailed access to previously avoided episodic memory content. It seems that after the perception of a potentially threatening cue, this voluntary memory search is helpful in evaluating the dangerousness of the stimulus on the basis of previous experiences including the traumatic events. This assumption is in line with current theories of emotional processing in PTSD that attribute changes in exposure therapy to the increasing ability to disentangle past experiences and current threat (Schauer et al., 2005). Accordingly, successful therapy counteracts attentional avoidance and enhances efficient memory retrieval so that patients are able to identify aversive stimuli as reminders of past experiences rather than as currently dangerous.

Furthermore, a significant increase of activity in left occipital brain regions during aversive stimulation from pre- to posttest was only found in the NET group. Several studies have reported reduced cortical reactivity to threat cues in PTSD patients compared to non-traumatized control subjects in posterior brain areas. Catani, Adenauer, et al. (2009) demonstrated that PTSD patients showed a significantly smaller affective modulation of occipital regions in response to aversive pictures as compared to control participants. Moreover, Felmingham et al. (2003) also found a reduced ERP signal in PTSD in response to affective faces. These results were interpreted as attentional disengagement or cognitive avoidance of aversive stimuli in PTSD. The finding that only treated patients showed an increase of activity in occipital brain regions after therapy can be interpreted as an enhancement of visual processing of threat cues. As the increase of occipital activity, however, did not reach significance in the Group $\times$ Time interaction in the permutation analysis, we have to be cautious about the interpretation of this result. Future studies are needed to replicate our findings with larger sample sizes.

Interestingly, the increase of occipital activation in the NET group was only present in the left hemisphere. This unilateral enhancement of cortical activity in treated patients is consistent with recent studies finding alterations of lateralization in PTSD (Rabe et

al., 2007; Metzger et al., 2004). While the left hemisphere is associated with approach motivation and verbal processing, the right hemisphere is associated with withdrawal motivation and nonverbal, perceptual processing (Davidson, Shackman, & Maxwell, 2004). In PTSD, trauma memory retrieval is mainly accompanied by right hemispheric activation explaining the nonverbal nature of intrusions and the fragmented, incoherent nature of trauma narratives (Brewin, 2007; Lanius et al., 2004). According to Brewin‘s dual representation theory of PTSD, our finding of increased left hemispheric activation in posterior areas after therapy might reflect a processing mechanism triggered by higher order, verbally mediated, and voluntary retrievable memories of the traumatic event (Brewin, 2007).

There are a number of limitations of the present study, which illustrate the challenges of studying neural correlates in a sample of severely traumatized participants. One limitation is the loss of MEG data sets of 15 participants after randomization procedure is quite high. These dropouts were mostly related to participants‘ refusal of MEG assessment, poor quality of MEG data, and participants’ inability to complete the study as a result of deportation due to a denial of asylum by the German authorities. Importantly, these participants did not differ in any clinical variable compared to the study completers. Moreover, none of the participant s dropped out of NET treatment voluntarily. Compared to average dropout rates of 20% during ongoing therapy reported in treatment studies using exposure and non-exposure treatments of PTSD (Grinage, 2003; Hembree et al., 2003), this finding is particularly noteworthy and shows that NET is well tolerated even by severely traumatized refugees with an unstable asylum status. Another limitation of this study is that a significant number of patients took antidepressant and neuroleptic medication. However, as there were no differences between treatment groups with respect to intake of medication, pharmacological effects as an alternative explanation for NET induced changes are improbable.

In summary, our findings indicate that Narrative Exposure Therapy causes an increase of parietal cortical activity related to the processing of aversive pictures that can be interpreted as a re-establishment of cortical top-down regulation of attention towards these stimuli. NET seems to induce an improvement of episodic memory retrieval that prevents treated patients from being overwhelmed by their own traumatic memories when confronted with aversive or threatening stimuli. Patient treated with NET are able to rely on more elaborate episodic memory contents. They are therefore enabled to re-appraise the direct danger of the current situation, thereby interrupting their former pathological defensive reaction.

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