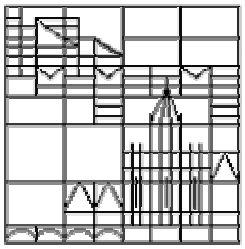

Characteristics of abnormal visual processing and recognition memory of affective pictures in PTSD

Dissertation

zur Erlangung des akademischen Grades des Doktors der Naturwissenschaften

an der Universität Konstanz

Fachbereich Klinische Psychologie und Neuropsychologie

vorgelegt von

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Tag der mündlichen Prüfung: 15.11.2006

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Acknowledgment

This study was conducted at the Department of Clinical Psychology and Neuropsychology, University of Konstanz under the supervision of Prof. Thomas Elbert and Prof. Johanna Kissler. I am grateful to Prof. Elbert for giving me the opportunity to realize my ideas for the present work and for providing me with all necessary means and resources. Further, his support in the planning and implementation of the study and his comments on prior versions of this manuscript were of great value. I further want to thank Prof. Kissler for her support in all phases of this project. Her advice in designing the experiment, and in the analysis of the data, as well as her inputs as regards content were invaluable. Thanks to all the members of the Psychotrauma Clinic for Refugees for their support in the recruitment and diagnostic exploration of the PTSD patients. Thanks also to the research ward of the Center for Psychiatry Reichenau for the help in the recruitment of the clinical control subjects. Special thanks also to Prof. Brigitte Rockstroh. Another big 'thank you' goes to our technical assistants Ursula Lommen, Bärbel Awiszus, and Christiane Wolf for their help in carrying out the many MEG measurements. Further thanks go to all the members of the research group who made me feel comfortable during my work. Thanks to all the subjects that readily took part in this study. Finally, a big hug goes to my parents Luise and Wolfram Borgelt for all their love.

Contents

Characteristics of abnormal visual processing and recognition memory of affective pictures in PTSD

Abstract

The present study was aimed at elucidating three characteristics of abnormal emotional processing in PTSD. A recognition memory paradigm was employed, in which emotional and neutral pictures from the International Affective Picture System (IAPS) were repeatedly shown to a group of Kurdish PTSD patients. Patients were victims of organized violence and torture. Healthy German and Kurdish subjects served as control groups. In addition, a clinical control group of Schizophrenic patients was tested. Stimuli were randomly presented with a duration of 1200ms and an interstimulus interval of 600ms. The first picture repetition occurred after 11s, the second repetition about 28min later. Participants were asked to memorize as many pictures as possible. Recordings of functional brain activation were made using a 148-channel whole-head magnetometer. Minimum Norm source localization procedures were applied to analyze the neuromagnetic data. A subsequent recognition memory task followed the MEG measurement to test for subjects' behavioral recognition performance.

First, evidence was found for an early, preconscious activation of a hypersensitive alarm system in PTSD in response to threatening stimuli. The first exposure to aversive pictures, compared to positive and neutral ones, elicited a significantly higher source strength in orbitofrontal brain regions of PTSD patients in the time interval from 90-120ms after stimulus onset. This enhanced source strength was positively correlated with the severity of arousal symptoms.

Second, support was found for a distorted mnemonic filter in the form of a lack of repetition suppression in PTSD. Healthy controls showed the expected decrease of source strength across the presentations of negative pictures, whereas PTSD patients responded with a slight increase 230-380ms after picture onset in the inferior frontal and anterior temporal cortices. Correlations were found with overall PTSD symptom severity. The observed effect might be due to a distortion or inhibition of the initial cortical response to the aversive pictures. The assumed strong subcortical

involvement in early initial evaluation of aversive pictures might interfere with subsequent cortical processing.

Third, PTSD subjects showed a selective long-delay activity enhancement in the temporal cortex in response to the repetition of negative pictures. This effect occurred 380 to 600ms after stimulus onset and reflects spreading activation in a sensitized emotional, sensory-perceptual fear memory network. Due to the associative character of this network it was hypothesized that new aversive stimuli can be easily linked to this network. This would be recognizable in a selective recognition facilitation for these stimuli. The data confirmed the hypothesis by showing no differences between all four groups in recognizing the negative pictures. Significant impairments were found for positive and neutral stimuli in the PTSD group, confirming earlier reports of non-trauma specific memory deficits in this disorder.

The finding of the hypersensitive alarm system is discussed with regard to its physiological basis. Implications for possible pharmacologic interventions are considered, which might contribute to a reduction of neuronal arousal, thereby playing an important role in the potential prevention and therapy of PTSD. Furthermore, the lack of repetition suppression and the selective activation of the emotional, sensory-perceptual fear memory network are discussed with regard to their relevance for the maintenance of PTSD. The first might contribute to the typically observed attentional bias in PTSD that is directed towards threat-related information. Implications for therapy are briefly discussed. The pronounced fear memory network represents a key feature for the explanation of reexperiencing symptoms in PTSD. The latter notion is supported by the correlation of severity of reexperiencing symptoms and the change in source strength in temporal brain areas.

Zusammenfassung

Die vorliegende Arbeit zielte darauf ab, drei charakteristische Merkmale abnormer emotionaler Verarbeitung bei PTSD-Patienten zu untersuchen. Ein Wiedererkennungsparadigma wurde verwendet, bei dem emotionale und neutrale Bilder aus dem International Affective Picture System (IAPS) wiederholt gezeigt wurden. Die untersuchten PTSD-Patienten waren Opfer organisierter Gewalt und Folter. Als gesunde Kontrollgruppen dienten zum einen eine Gruppe deutscher Probanden, zum anderen eine Gruppe kurdischer Personen. Zusätzlich wurde eine klinische Kontrollgruppe schizophrener Patienten untersucht. Die Stimuli wurden in zufälliger Reihenfolge dargeboten. Die Präsentationsdauer pro Bild betrug 1200ms mit einem Interstimulusintervall von 600ms. Die erste Bildwiederholung erfolgte nach 11 Sekunden, die zweite Wiederholung nach etwa 28 Minuten. Die Teilnehmer der Studie sollten so viele Bilder wie möglich im Gedächtnis behalten. Die funktionale Gehirnaktivität wurde mittels eines 148-Kanal Ganzkopfmagnetometers gemessen. Bei der Analyse der Daten wurden Minimum-Norm Verfahren zur Quelllokalisation verwendet. Im Anschluss an die MEG-Messung erfolgte ein Wiedererkennungstest, der die Wiedererkennungsleistung der Probanden untersuchte.

Es wurden Hinweise für ein frühes, vorbewusstes, hypersensitives Alarmsystem bei PTSD-Patienten gefunden, was durch die bedrohlichen Bildreize aktiviert wurde. Bei der ersten Darbietung negativer, im Vergleich zu positiven und neutralen Bildern, zeigten PTSD-Patienten eine signifikant höhere Quellstärke in orbitofrontalen Regionen im Zeitintervall von 90-120ms nach Stimulusbeginn. Diese Aktivierung korrelierte mit dem Schweregrad der Erregungssymptome.

Weiterhin wurden Hinweise für einen abnormen Gedächtnisfilter in Form einer fehlenden Unterdrückung von neuronaler Aktivität bei der Wiederholung von Bildreizen gefunden. Gesunde Probanden zeigten die erwartete Abnahme der Quellstärke über die drei Wiederholungen der negativen Bilder hinweg, während PTSD-Patienten durch eine leichte Zunahme der Quellstärke im inferioren Frontalkortex und im anterioren Temporalkortex im Zeitintervall zwischen 230-380ms gekennzeichnet waren. Ferner wurden Korrelationen mit der PTSD Gesamtsymptomschwere gefunden. Möglicherweise kommt der gefundene Effekt dadurch zustande, dass der Kortex bei der ersten Darbietung der negativen Bilder

gehemmt wurde, bzw. dass die kortikale Verarbeitung mit einer primär subkortikalen Verarbeitung interferiert hat.

Darüber hinaus konnte gezeigt werden, dass PTSD-Patienten in einem Zeitbereich zwischen 380 und 600ms nach Stimulusbeginn eine selektive Antwortverstärkung im Temporalkortex auf die negativen Bilder hin aufweisen. Diesem Effekt liegt eine sich ausbreitende Aktivierung in einem hypersensitiven Furchtnetzwerk zugrunde. Aufgrund des assoziativen Charakters dieses Netzwerkes wird die Hypothese aufgestellt, dass neue aversive Reize problemlos mit dem Netzwerk verknüpft werden, was sich in einem selektiven Wiedererkennungsvorteil für diese Bilder widerspiegeln sollte. Diese Hypothese wurde durch die Ergebnisse aus dem Wiedererkennungstest gestützt. Alle vier Gruppen zeigten dieselbe gute Leistung bei der Wiedererkennung aversiver Bilder. Bei der Wiedererkennung positiver und neutraler Reize zeigten die PTSD-Patienten deutliche Beeinträchtigungen. Dieser Befund steht in Einklang mit nicht-Trauma bezogenen Gedächtnisdefiziten.

Die physiologischen Grundlagen des hypersensitiven Alarmsystems werden diskutiert. Es werden mögliche pharmakologische Interventionen, die zu einer Verminderung der neuronalen Erregung und damit eventuell zu einer Prävention und Therapie der PTSD beitragen können, erörtert. Weiterhin werden die fehlende neuronale Inhibition bei Reizwiederholung und die selektive Aktivierung des assoziativen Furchtnetzwerkes im Hinblick auf die Aufrechterhaltung der Störung diskutiert. Die fehlende neuronale Inhibition steht möglicherweise mit der häufig bei PTSD-Patienten beobachteten Aufmerksamkeitsverzerrung zugunsten bedrohlicher Reize in Zusammenhang. Implikationen für die Therapie werden erörtert. Schließlich wird diskutiert, inwiefern das ausgeprägte Furchtnetzwerk für die Erklärung der Wiedererlebenssymptome von PTSD-Patienten herangezogen werden kann. Der postulierte Zusammenhang wird durch die Korrelation zwischen der Schwere der Wiedererlebenssymptome und dem Anstieg der Quellstärke in temporalen Hirnarealen gestützt.

1 General introduction

1.1 PTSD symptomatology

Abram Kardiner (1941) was one of the first authors defining the symptomatic complex of post-traumatic stress disorder (PTSD). He called it a “physioneurosis” in which victims suffer from “an enduring vigilance for and sensitivity to environmental threat”. Kardiner described the patients’ physiological hyperarousal that occurs in response to sensory-perceptual stimuli from different modalities. He noted that “from a physiologic point of view there exists a lowering of the threshold of stimulation; and, from a psychological point of view, a state of readiness for fright reactions”. Patients are supposed to remain constantly alert for the return of the trauma.

PTSD can develop after a person has been exposed to a traumatic life event. During this event the person responds with intense fear, helplessness, or horror. Subjectively, the victim experiences a severe threat for his/her self or others. Examples of such events are combat experience, rape, attacks, torture, or severe accidents. Sometimes it is sufficient to be a witness of such events for the development of PTSD. The core symptom of PTSD according to DSM-IV (APA, 1994) is to persistently relive the traumatic event. Intrusive recollections include images, thoughts, or perceptions, as well as nightmares or even flashbacks. Furthermore, patients show strong avoidance of trauma associated stimuli and numbing of general responsiveness. Finally, victims show an increased physiological arousal, observable in hypervigilance or an exaggerated startle response. The avoidance behavior and the emotional numbing can be interpreted as a compensation for the chronic hyperarousal. Numbing of responsiveness to the environment and intermittent episodes of hyperarousal in response to emotionally arousing stimuli alternate in chronic PTSD. A chronic form of PTSD exists when symptoms last longer than six months. The disorder causes a severe impairment of the victims’ overall quality of life.

The disorder goes along with the development of a range of biological abnormalities, although it is unknown whether some of these distinctive features represent a specific vulnerability for the development of PTSD rather than a consequence. Alterations in various biological systems have been found, including

psychophysiology, neurotransmitter systems, the hypothalamic-pituitary-adrenal axis, memory systems, and neuroanatomy (for a review see van der Kolk, 2001).

1.2 Perspective and focus of the present study

In the present work it is hypothesized that PTSD is a disorder of distorted memory systems. A disconnection of the declarative context memory, termed “cold memory”, (Metcalfe & Jacobs, 1996) and the non-declarative emotional and sensory-perceptual “hot” memory system is supposed to underlie the core symptoms of PTSD (see also Elbert et al., 2006). It is hypothesized that these plastic changes in the brain circuitry through stressful, traumatic experiences are more pronounced in victims with severe cumulative trauma exposure. According to the building-block effect (Neuner et al., 2004) the number of traumatic event types predicts psychological strain. Frequency of intrusions, hyperarousal, and avoidance were all found to be correlated with the number of reported events in a large sample of refugees affected by civil war. The underlying brain mechanisms are also assumed to be more affected. Therefore, the present study aimes to elucidate three aspects of mnemonic processing in a group of severely traumatized PTSD patients. The first investigated aspect is not a mnemonic process per se, but is supposed to influence successive memory processing. Evidence was sought for:

1.) a fast and rapidly acting sensitized brainstem-amygdala-cortical alarm system. The early activation of this system commences a successive prioritized information processing in favour of threatening stimuli. Once the alarm system is active, subsequent processing might be sensitive for threatening stimuli.

2.) a distorted mnemonic filter that allocates attentional resources and orientation towards threatening stimuli. This filter is represented in the mechanism of repetition suppression.

3.) a selective sensitivity of brain networks involved in the retrieval of aversive trauma-related information from the “hot” memory system. Trauma- or threat-related triggers are thought to activate strong autonomous “hot” memories from a fear network. Due to the network’s associative character, threat-related trigger stimuli are easily linked to it. The consequence should be an enhanced recognition memory for aversive stimuli.

These aberrations from normal mnemonic processing, compared to non-PTSD subjects, are hypothesized to contribute to the maintenance of PTSD.

1.3 A cognitive model of PTSD

According to the cognitive model of PTSD proposed by Ehlers and Clark (2000), chronic PTSD develops when a victim (re-)processes a traumatic event or its consequences in the way that he/she experiences a serious, present threat. Two factors seem to contribute to this experience. The persisting experience of a present threat contributes to chronic physiological stress reactions that are supposed to alter functional alarm- and mnemonic systems in the brain.

The first contributing factor for chronic PTSD is a dysfunctional appraisal of the trauma and its consequences. The experience of a present threat (e.g. fear of not reaching important goals in life) arises from the inability to regard the traumatic event as a single event of the past. Thus, the traumatic incident stays affiliated with the presence. The trauma is overgeneralized to activities, which the victim performed without any concerns prior to the trauma, but that now are regarded as dangerous. As a consequence these activities will be avoided in future. Similarly, internal attributions are generated that are characterized by the belief that the trauma is confounded with the subject's personality. This leads to overgeneralized anxiety and avoidance. Furthermore, the consequences of the trauma are negatively evaluated. The PTSD symptoms are regarded as everlasting and represent a significant impairment of the physical and psychological well-being. Reactions of the social environment are negatively evaluated, too. The victim feels isolated and not accepted by others. Consequences are negative emotions like fear, depression, shame, guilt, and anger. Dysfunctional coping strategies further enhance these effects. Sometimes the experienced threat in the presence is further strengthened by the belief that the worst is still to come.

Beside a dysfunctional appraisal process, a second trigger contributes to the experience of a present threat, namely the features of memory for the traumatic event. The trauma memory is characterized by a massively disturbed intentional recall and fragmentation. The traumatic event is isolated from the usual spatial and temporal episodic context. The temporal order of events is also distorted. At the

same time, intrusive memories are elicited by stimuli that have become temporally associated with the trauma. This is also true for associated emotional states. Intrusions are characterized by multimodal sensory-perceptual impressions rather than thoughts. They resemble a strongly emotional re-experiencing of the trauma. Sometimes the victim is unaware that these are memories. In case of these 'flashbacks', the sensory impressions are experienced as if they are happening again, rather than being memories from the past. The accompanying emotions are the same as the original ones at the time of the trauma. According to Krystal et al. (1998) this is due to the fact that the organizing and structuring executive mechanisms, normally provided by frontal brain areas, are impaired. The frontal cortex is involved in networks that comprise the amygdala, the mediodorsal thalamus, and the hippocampus. Stimulation of the hippocampus can lead to memory retrieval that takes place without the involvement of frontal executive functions. The memory that is retrieved under these conditions resembles the memories of PTSD patients. Stimulation of the hippocampus produces memory retrieval that is similar to the nature of flashbacks. It is characterized by reduced mnemonic flexibility (Moscovitch, 1992). Retrieval strategies involving the hippocampus are cue dependent, rather than strategic. The frontal cortex is responsible for the organizing and strategizing processes. Hippocampal stimulation and flashbacks are memory retrieval conditions that bypass the frontal executive component. Both conditions share the quality of the memory of being reexperienced rather than recalled (Halgren, 1978; Gloor, 1982). The occurring experiential phenomena have polysensory characteristics. Intrusions are normally accompanied by the same emotions and stress reactions that were present at the time of the trauma. Every re-experiencing is associated with a similar physiological reactivity. Sensory experiences can also occur in isolation, without a conscious recollection of the traumatic event itself. Impairments in intentional recollection together with intrusive memories are experienced as disturbing for the victims and contribute to the experience of a present threat.

The dysfunctional appraisal style and the specific nature of the trauma memory cause the subjective experience of a present threat in PTSD patients. This chronic state contributes to alterations in peripheral and brain physiology, thereby affecting alarm- and mnemonic systems. The investigation of abnormalities in the brain's alarm- and mnemonic systems in PTSD are in the focus of the present study.

1.4 The physiological stress reaction in PTSD

The physiological basis of the stress reaction consists of sympathetic nervous system responses on the one hand and of the activity of the hypothalamic-pituitary-adrenocortical (HPA) axis on the other hand. The latter is described in more detail.

When stress is experienced, the hypothalamus releases corticotropin-releasing factor (CRF) that in turn activates the pituitary gland to increase the secretion of adrenocorticotropin hormone (ACTH) (Delbende, 1992). Subsequently, ACTH stimulates the release of cortisol from the adrenocortical cells (Owens, 1991). For a long time, it was thought that the animal model of chronic stress might be transferable to PTSD. In animals chronic stress leads to persistent hyperactivity of both the HPA axis and the sympathetic nervous system. Furthermore, alterations in the monoaminergic neurotransmitter system and degenerative structural processes in the hippocampus have been observed in chronically stresses animals. Antidepressant drug treatment normalizes some of these parameters that have also been found in depressive patients (Fuchs, 2002). However, more recent studies suggest significant differences between the physiology of chronic stress and PTSD (Yehuda, 1998). Regarding the neuroendocrinology of PTSD, Yehuda suggests the following model: unlike in depression, lowered basal cortisol levels (Yehuda, 1996a; Kellner, 2002; Bremner, 2003; Wessa, 2006), an increased sensitivity of the glucocorticoid receptors (Yehuda, 1995; 1996; 2004), and a higher sensitivity of the negative feedback loop that is responsible for the regulation of the hypothalamic-pituitary-adrenocortical system (see Yehuda, 2002) have been found in chronic PTSD. Figure 1 contrasts the HPA stress response of healthy subjects, patients with depression, and PTSD.

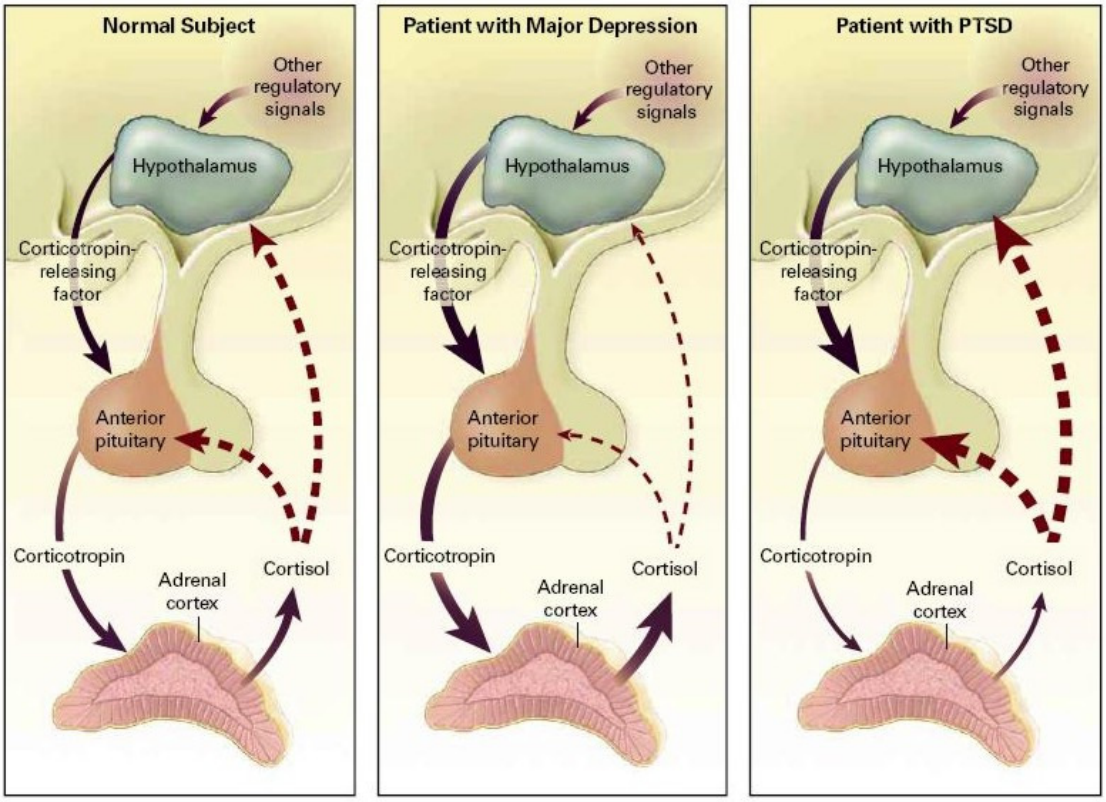


Figure 1: Stress responses in healthy subjects, patients with major depression, and patients with PTSD. PTSD patients are characterized by low cortisol levels and high levels of CRF. Furthermore, in these patients the negative feedback loop that is responsible for the regulation of the hypothalamic-pituitary-adrenocortical system is hypersensitive (Figure taken from Yehuda, 2002).

Additional proof for the hypothesis of chronically reduced cortisol levels independent of trauma type, but correlated with symptom severity, arises from other authors (e.g. Goenjian et al., 1996; Neylan et al., 2005). Stein et al. (1997) showed that the number of glucocorticoid receptors is elevated in PTSD patients. Cortisol secretion activates the negative feedback loop and thereby stopps secretion when cortisol binds to hypothalamic receptors. Contrary to depression, where this 'shutdown' mechanism is supposed to be distorted, this pattern was not found in PTSD. Instead, a hypersensitive negative feedback loop is suggested for PTSD (e.g. Stein, 1997b). Evidence exists that CRF is chronically elevated in PTSD (Bremner, 1997). At first glance this seems paradoxical given the low cortisol concentrations. This problem can be solved assuming that the sensitivity of the mentioned "shutdown" mechanism is increased in PTSD. The elevated secretion of CRF from the hypothalamus leads to adaptations in the pituitary gland. It reduces the release of ACTH resulting in

decreased cortisol levels. To compensate this low cortisol level, glucocorticoid (cortisol) receptors enhance their sensitivity and number (Yehuda, 1998).

The magnitude of the stress response is not solely measured by the absolute cortisol level. More important is the fluctuation of the cortisol concentration between baseline and stressful situations. It has been demonstrated that these fluctuations are significantly higher in PTSD patients compared to healthy controls in both pharmacological and non-pharmacological stress challenge studies (de Kloet, 2005). This means that the stress system is hyperresponsive in PTSD. Despite a normal or even lower than normal baseline cortisol level in PTSD, the response to stress is stronger than in healthy individuals due to higher numbers and sensitivity of glucocorticoid receptors. The sensitization of the HPA axis is responsible for the unusually heightened response to stress. Symptoms of increased startle, hypervigilance, and physiologic arousal can be explained by this model.

The hypersensitive stress system in PTSD with its subsequent transmitter release cascades (e.g. CRF) contributes to the development of a hypersensitive alarm system.

1.5 Trauma memory lacks a spatial and temporal context

The absence of the ordering and structuring executive frontal brain function at the time of recollection is only one influencing factor of the intrusive nature of trauma memory. One additional factor is that trauma memory is not encoded with contextual information of space and time. Usually new episodic memory is integrated into an already existing episodic memory base that is hierarchically organized with specific relations to life episodes and topics (Conway, 2000a). The contextual integration is provided by hippocampal structures (e.g. Gewirtz, 2000). In healthy subjects “cold“ memories are connected with “hot” memories, whereas the latter become autonomous in PTSD patients and form an isolated fear network (Lang, 1979). The current published literature suggests that highly increased cortisol levels released in response to the traumatic event cause neurotoxicity and a functional impairment of the hippocampus (e.g. Sapolsky, 1992). However, as outlined above, cortisol levels are not elevated in chronic PTSD. Even in the acute aftermath of a trauma, cortisol levels are not significantly elevated (McFarlane, 1997; Resnick, 1995). Therefore it is

hypothesized that hippocampal glucocorticoid receptors show an increased sensitivity and increase in number (Liberzon, 1999a). Such an excessive glucocorticoid receptor activity can result in an atrophy of dendrites of pyramid cells in the hippocampus. Additionally, glucocorticoids suppress the neurogenesis in the gyrus dentatus and modulate the excitability of hippocampal neurons (for an overview see McEwen, 1999).

Altogether, acute traumatic stress and subsequent stressful symptoms of PTSD together with the described physiological mechanisms are likely to impair the function of the hippocampus. In this state, contextual information is insufficiently encoded not only at the time of the trauma, but also at the time of retrieval. This contributes to intrusive, sensory-perceptual trauma memory that can have 'here-and-now' quality in case of flashbacks.

In the long run another factor is likely to contribute to the disconnection of "hot" emotional, sensory-perceptual representations of the trauma and the "cold" declarative context memory. In victims of multiple traumatic experiences the high number of events provides more and more conflicting information. Typically, a person can only retrieve one context in which the fear network was previously activated. With an increasing number of traumatic events, the associative fear network expands and interconnections becomes stronger. This process is promoted by the coactivation of plasticity-enhancing motivational and reward systems during the traumatic events. In parallel, the likelihood of the coactivation of the declarative memory system decreases, thereby further advancing the separation of the two memory systems (e.g. Elbert et al., 2006).

1.6 Contributions of chronically elevated CRF levels to the development of a hyperresponsive amygdala

The amygdala is responsible for evaluating the affective salience of a sensory stimulus (LeDoux, 2000). In several imaging studies activity of this structure has been associated with various aversive affective states like fear and anxiety (Furmark, 1997; Critchley, 2002), but also with appetitive responses (Maren, 2003). When stress is experienced, CRF is released to the amygdala (Merlo, 1995). CRF is essential for many of the endocrine, autonomic, and behavioral responses to a

variety of stressors (Dunn, 1990). CRF secretion seems to be chronically elevated in PTSD (Bremner, 1997). Acute CRF receptor activation in vitro increases the excitability of the basolateral amygdala (BLA) (Rainnie, 1992). Rainnie et al. (2004) further demonstrated that the injection of a potent CRF agonist over several consecutive days into the BLA leads to long lasting anxiety-like responses in behavioral tests. These responses persisted for weeks. The authors suggested that the application of the agonist induced plastic synaptic changes dependent on the activation of an NMDA receptor-mediated CaMKII-dependent second messenger cascade. They also demonstrated hyperexcitability of the BLA via whole-cell patch-clamp recordings. As a consequence of the CRF agonist priming, a lactate sensitivity developed. Sodium lactate is an anxiogenic agent that elicits autonomic fear reactions. Lactate sensitivity is also a clinical feature of PTSD patients (Jensen, 1997).

In summary, the following conclusions can be drawn for PTSD. Due to the chronically elevated CRF concentrations, plastic synaptic changes take place in the amygdala that are associated with hyperexcitability. When confronted with stressful stimuli, an enhanced autonomic and behavioral fear response is elicited. In the central nervous system, processes in which the amygdala is involved, like emotional modulation of sensory cortices (see below), are influenced by the hypersensitive amygdala activity.

1.7 Contributions of chronically elevated norepinephrine levels to a hyperresponsive amygdala

CRF mediated plastic changes in the amygdala are not the only mechanisms by which a hypersensitive amygdala develops. Chronically elevated norepinephrine concentrations in the central nervous system of PTSD patients play also an important role.

The locus coeruleus/norepinephrine (LC/NE) network has the function of a generalized warning system that helps determining whether an individual turns attention to potentially threatening stimuli (Nakamura, 1990). Axons from the LC spread to the whole cerebral cortex and to subcortical areas including the hippocampus, amygdala, thalamus, and hypothalamus. NE projections also exert an

excitatory influence on the HPA-axis. Acute stressors promote an increased firing rate of LC neurons and thereby induce a rapid increase of NE release (Levine, 1990).

In patients with chronic PTSD, Geracioti et al. (2001) have measured central nervous system (CNS) NE-levels through an indwelling subarachnoid catheter. Compared to healthy controls they found a significantly higher baseline CNS noradrenergic tone that was further correlated with the severity of PTSD symptoms. In line with these findings is the work of Charney et al. (1995) who noted a sustained hyperactivation of CNS fear-related neurocircuits in PTSD at baseline condition.

A chronically increased NE-level impairs the function of the prefrontal cortex (PFC). The prefrontal cortex is involved in complex stimulus discrimination, working memory, learning, problem-solving, and most importantly in this context it has an inhibitory influence on the amygdala. Thus, the PFC is crucial for the inhibition of irrelevant stimuli and responses. NE can impair the normal functioning of the PFC via binding on alpha-1 receptors. It is also able to enhance the functioning via binding on alpha-2 receptors. The affinity of NE is higher for alpha-2 receptors. This means that at low to medium stress levels prefrontal functioning is enhanced. When NE-levels rise, the transmitter increasingly binds on alpha-1 receptors, thereby distorting prefrontal functioning. An U-shaped dose effect of arousal on performance was first formulated in the Yerkes-Dodson law (Yerkes, 1908). The impairing effect might be found in PTSD due to the chronically elevated NE concentrations. The inhibiting influence of the PFC on the amygdala becomes weaker, and this contributes to the hyperreagibility of the amygdala.

1.8 Conclusions

In the context of the present study the hypothesized hypersensitive amygdala of PTSD patients plays a crucial role. The amygdala activation influences early stages of information processing, memory encoding, and retrieval. Before an environmental threat-stimulus enters consciousness, its valence is already evaluated by the amygdala. As will be described later, amygdala modulation of orbitofrontal cortex (OFC) takes place. The OFC rapidly makes a choice for an adequate behavior in the presence of a threatening stimulus. An exaggerated pre-conscious amydgala and

OFC response to threatening stimuli is hypothesized in PTSD. This bias is likely to influence further stages of information processing.

In the case of PTSD, attentional resources are suggested to stay focussed on threatening stimuli, thereby neglecting other contextual information. A healthy subject is able to process both kinds of information in parallel, the threatening stimulus and contextual information, and shows some form of habituation-like response to repeated presentations. In contrast, PTSD patients suffer from a distorted mnemonic filter that inhibits adaptation to the threatening stimulus, thereby occupying attentional resources, which makes it more difficult to integrate contextual information.

Exposure to a threatening stimulus will activate associated “hot” memory percepts in PTSD patients. An exaggerated amygdala activity enhances arousal in brain areas that store the perceptual representations of traumatic events. Thus, the fear network will be highly active and the trigger stimulus can be integrated into this memory network by association. The consequence should be an enhanced recognition memory for this stimulus.

2 An early rapid brainstem-amygdala-cortical alarm system

From an evolutionary viewpoint it is essential for an organism to respond rapidly to threat-related signals in the environment. Therefore an automatic, pre-attentional alarm system is desirable that is able to quickly initiate a fight-/flight response. Liddell et al. (2005) proposed such an evolutionary adaptive neural alarm system that makes rapid alarm responses to signals of threat without the need for a conscious appraisal of the threat (see Figure 2). Visual sensory information enters the superior colliculus in the brain stem via direct projections from the retina (Morris, 1999; Vuilleumier, 2003). The retinal ganglion cells that build the connection with the colliculus have large, fast conducting axons. In contrast, the axons connecting the retinal cells with the lateral geniculate nucleus (and thus with the striate cortex) are smaller and slower (Schiller, 1977). The fast axons are the basis for rapid inputs to subcortical areas in response to salient visual stimuli. The superior colliculus serves to control goal directed orientation towards novel stimuli (Morris, 2001) and it has projections to the thalamic pulvinar (Benevento, 1975). Together, the colliculo-pulvinar complex represents a secondary visual pathway beside the primary system that consists of the thalamic lateral geniculate nucleus and the striate cortex. The pulvinar has tight connections with the amygdala (Amaral, 1992) that sends signals about the significance of a stimulus to the LC. Pulvinar and amygdala form a functional unit, generating responses to visual threat (Ward, 2005). As Morris et al. (1997) demonstrated, increasing salience of a stimulus is associated with increasing pulvinar activity. Moreover, pulvinar activity was shown to be positively correlated with amygdala activity. The LC represents the brain's most important 'supplier' of noradrenergic input for diverse cortical areas, including particularly frontal regions (Jones, 2003). In addition, excitatory projections reach the amygdala, pulvinar, and superior colliculi (Berntson, 2003; Jones, 2003). The LC with its ascending excitatory noradrenergic pathways fulfills the function of a brainstem arousal system. Whereas the pulvinar and the superior colliculus are responsible for automatic orienting within the overall alarm reaction, the LC with its excitatory efferents to the cortex is concerned with the alerting complex (Posner, 1997). Whenever a stimulus is tagged as 'salient', areas in the frontal cortex are stimulated via the noradrenergic inputs to promote the rapid further evaluation of the stimulus. Thereby an accelerated increase in alertness is achieved and threatening stimuli are rapidly and efficiently processed.

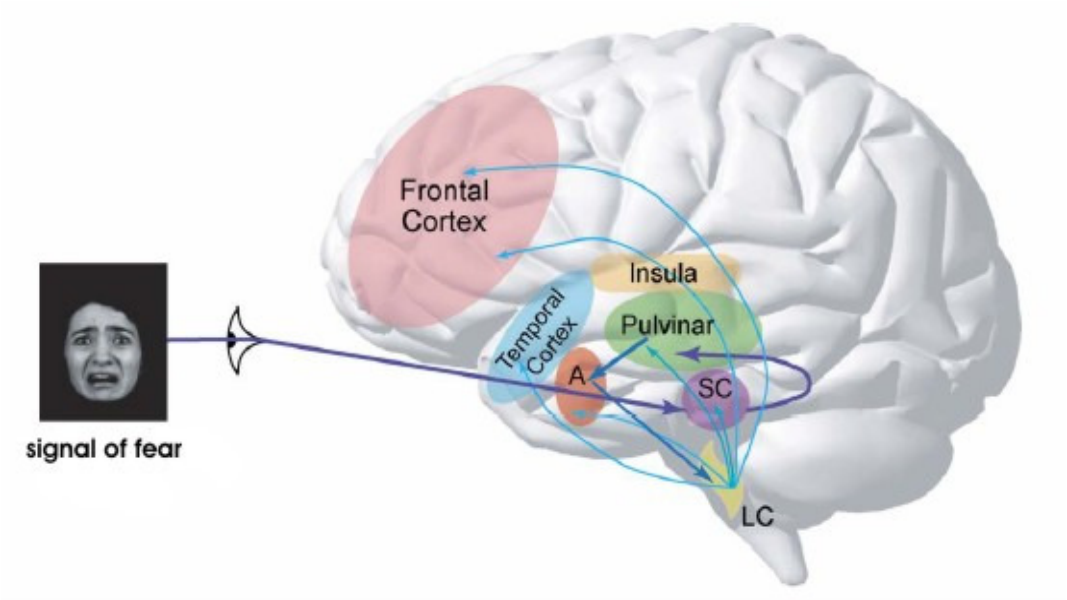


Figure 2: The brainstem-amygdala-cortical alarm system as proposed by Liddell et al. (2005).

Thus, nature provides an automatic, pre-attentional alarm system that allows to detect significant stimuli in the environment before a higher cognitive appraisal process is initiated. An organism can rapidly initiate a flight-/fight response to threatening stimuli that might endanger survival. In subjects that have a lot of experience with threatening stimuli, like in PTSD, this alarm system might be hypersensitive.

One goal of the present study is to elucidate the exact activational onset of the supposed hypersensitive alarm system in PTSD when exposed to threatening stimuli.

2.1 Rapid affective processing without conscious awareness via an extrastiate visual pathway

2.1.1 Affective modulation in blindsight

Liddell's model postulates a direct route for crude visual information to the amygdala that, for emotional evaluation, is independent of processing in the primary visual cortices. Parrallel to the lateral geniculate nucleus-striate cortex-amygdala processing stream that is activated whenever there is a conscious visual and emotional percept (Adolphs, 2002), a secondary visual pathway that operates on a

pre-attentional and more rapid level is present. This alternative route is best investigated in patients with blindsight. Morris et al. (2001) measured differentiated amygdala activation in a blindsight patient (G.Y.) who suffered from a right homonymous hemianopia after lesions in his left occipital cortex (V1). Presentations of fearful and happy faces in the blind visual hemifield resulted solely in a general awareness that something had happened, but not in a conscious perception of the faces. fMRI (functional magnetic resonance imaging) recordings showed an increased bilateral amygdala response only for fearful faces. In addition, a covariation between activity in the amygdala and the superior colliculus was revealed. In a second aversive conditioning experiment, an angry male and female face were presented in the blind and the intact hemifield. The presentation of the female face (CS^+) in the intact hemifield was always paired with an aversive noise burst. When in the test phase the female face (without noise) was presented to the blind hemifield, bilateral amygdala activity was enhanced compared to the angry male face. Further, activity covaried between right amygdala and the pulvinar when the subject was confronted with the 'unseen' CS^+. Similar to the first experiment the superior colliculus showed a higher activity in response to the 'unseen' CS^+ compared to the 'unseen' male face. This study gives evidence for differential subcortical responses to emotionally salient stimuli without conscious perception. The brain structures subject to emotional modulation are the superior colliculus, the pulvinar, and the amygdala.

The same blindsight patient was tested by de Gelder et al. (1999) for emotion recognition in different behavioral experiments. Video fragments were used as stimuli with a female speaker articulating the same sentence with different facial expressions (happy, sad, angry, fearful). It was shown that the subject correctly guessed facial expressions of either happy/sad, angry/sad, or angry/fearful stimulus pairs that were presented to his blind hemifield. In a more complex four-alternative forced-choice paradigm it was ensured that his good performance was due to a covert emotional recognition and not due to a mere discrimination of two different movement patterns. Again, the patient made correct labelings of the four different emotional expressions, which were above chance level. In none of the experiments the patient reported a conscious perception of the faces. However, he was able to correctly guess the emotional valence based on crude subcortical visual and emotional processing.

The above described studies show that an unconscious emotional appraisal takes place. Morris (2001) also showed in his conditioning study that an even wider spectrum of emotional functions is accomplished without detailed analyses in the visual cortex. Intact fear conditioning to a visual cue despite complete bilateral cortical blindness after stroke was demonstrated by Hamm et al. (2003). The authors also showed that 'unseen' stimuli are sufficient to initiate reflexive behavioral responses to threat.

These findings strengthen the idea of a parallel neural pathway that is able to process threat-related stimuli independent of the lateral geniculate nucleus-striate cortex-amygdala stream and independent of conscious awareness.

Further proof for this secondary visual pathway arises from studies that show cortex-independent visual processing ability in macaques (Rodman, 1989) and humans (Sahraie, 1997) involving the superior colliculus. Sahraie stimulated both the blind and the sighted hemifield with a moving dot target and requested the subject to signal whenever he/she was aware of the stimulus. Next to the detection of an emergence of the colliculus during the 'unaware' stimulation they found a shift in the activity pattern from dorsolateral prefrontal areas in the 'aware' stimulation to medial- and orbitofrontal areas in the 'unaware' stimulation in both hemifields.

Summarizing, it has been demonstrated that an emotional appraisal of visual stimuli takes place even before consciousness comes into play. A detailed visual analysis in the striate cortex is not necessary for this appraisal. Furthermore is has been shown that reflexive behavioral responses are initiated on the basis of this pre-conscious evaluation process.

2.1.2 Simulated blindsight in healthy subjects using a backward masking paradigm

Studies with patients need further validation from studies with healthy subjects. Some similarities exist between the unconscious emotional stimulus processing in blindsight patients and the recognition of emotional cues in healthy subjects in a paradigm called 'backward masking'. In backward masking a very brief presentation of a target stimulus is followed by a second 'masking' stimulus. With specific interstimulus intervals, the masking stimulus effectively prevents a conscious

recognition of the target. Whalen et al. (1998) successfully employed the backward masking paradigm to show the differentiated amygdala response to fearful and happy faces. Affective slides (targets) were presented for 33ms each, followed by a 167ms presentation of a neutral face (mask). No interstimulus interval was used to ensure that subjects had no awareness of the negative and positive targets (Esteves, 1993). fMRI were recorded for 10 alternating epochs of blocked presentations of negative or positive targets. After recording, subjects were debriefed and questioned whether they had seen negative or positive faces. Participants only reported the neutral masks, but not of any of the targets. However, the measured BOLD (blood oxygen level-dependent) signal in the amygdala was significantly higher for the masked fearful faces than for the happy ones. Except a significant activity in the inferior prefrontal cortex, an impressive relative lack of activation was observed across all other brain regions.

Morris et al. (1999) demonstrated in a PET (positron emission tomography) study the activation of brain areas involved in the subcortical processing of masked visual stimuli in healthy subjects. When an CS^+ was paired with a loud aversive noise burst, higher skin conductance and right amygdala activity were measured when in subsequent test trials a neutral target stimulus was preceded by the masked CS^+ of which the subjects were not aware. In addition, the authors found a positive covariation of activity in the pulvinar and superior colliculus. Covariation of activity in different brain areas is a sign of functional connectivity. The conclusion of this study was that visual fear stimuli can be unconsciously detected by a colliculo-pulvinar-amygdala pathway that circumvents striate cortex. This pathway is also able to activate autonomic responses like skin conductance.

The two described studies demonstrate that an unconscious emotional appraisal of visual stimuli with subsequent autonomic responses takes also place in healthy subjects.

2.1.3 Conclusions about the extrastriate visual pathway

These findings from blindsight patients and backward-masking experiments emphasize that an initial response to emotionally salient stimuli does not require conscious awareness (Zajonc, 1980). The amygdala rapidly and automatically

verifies the affective valence of a stimulus prior or in parallel to an elaborate cortical processing (LeDoux, 1996). The complete secondary visual pathway consists of retinal ganglion cells with large, rapidly conducting axons (Schiller, 1977) that are connected to the superior colliculus (Vuilleumier, 2003). From there, crude visual information is transferred to the pulvinar and finally to the amygdala for emotional appraisal (Ward, 2005). Cells in the colliculus, pulvinar, and amygdala show covarying activity and emotional modulation (Morris, 1999; 2001). The entire process is fast, automatic, and without conscious awareness. In the backward masking paradigms, target stimuli were briefly presented for 33ms. This time was sufficient for a differentiated amygdala response. The amygdala further sends information about the significance of a stimulus to the locus coeruleus and the frontal cortex. The LC serves as a brainstem alarm system that has efferent noradrenergic connections to the cortex, including frontal regions. The involvement of frontal areas in the rapid and early processing of emotionally salient stimuli was already indicated by the significant activity of inferior prefrontal cortex (Whalen, 1998). Preconscious processing seems to involve particularly the orbitofrontal areas (Sahraie, 1997). The role of the amygdala and orbitofrontal cortex will be discussed in the following sections.

2.2 Role of the amygdala in fear

2.2.1 General function of the amydala

For survival it is important to adapt to situations that are potentially life-threatening. It is necessary to rapidly process environmental stimuli that signal danger and threat and to immediately initiate an effective defensive reaction (fight or flight) (e.g. Lang et al., 2000). A “fear module” tailored to meet these requirements is characterized by selectivity with regard to threatening input, automaticity, efficient attention capture, and relative resistance to cognitive influences. Furthermore it needs a specific neural basis (Öhman, 2001). A core structure in the brain fulfilling these requirements is the amygdala. Support comes from animal and human studies with patients suffering from brain lesions, as well as from stimulation and neuroimaging experiments. A meta-analysis of emotional activation studies employing PET and fMRI points to the specific role of the amygdala in the context of fear (Phan, 2002) .

2.2.2 Findings from animal lesion studies

Already in 1956 Weiskrantz compared the behavior of monkeys in a conditioned avoidance and conditioned depression experiment pre and post ablation of the amygdaloid complex. In the conditioned avoidance task, animals learned to associate the dark compartment of a shuttle box with an electric foot shock. This shock could be avoided by moving to the light compartment. For the conditioned depression task animals were trained to press a lever for a food pellet reward. Later a buzzing sound predicted a short time interval, in which lever pressing was followed by either an aversive loud noise or electric shock. Animals were required to suppress lever pressing during this time interval to avoid the aversive consequences. The extinction phases for both tasks were similar to the acquisition except that no aversive stimuli were presented. In the experimental group the amygdalectomy resulted in more rapid extinction of the conditioned avoidance and depression and in a slower rate of acquisition of the required behaviors compared to a healthy control group. In addition, general observations of behavior pre and post ablation showed a lack of fear or 'tameness'. Usually monkeys show escape responses, grimacing, or screeching towards man as signs of fear. They also show violent behavior towards conditioned aversive stimuli like laboratory gloves or sticks. After ablation, monkeys permitted petting and handling without signs of fear. They approached researchers and handled and chewed formerly aversive stimuli like laboratory gloves. The authors proposed that after amygdalectomy it becomes difficult for the animals to establish or recognize reinforcing stimuli, positive as well as negative. Motivationally relevant stimuli were not discriminated anymore which resulted in the observed fearlessness, lack of emotional conditioning, and accelerated extinction.

Other studies confirmed the essential role of the amygdala in the acquisition and expression of fear. Muller (1997) temporarily inactivated the lateral and basal nuclei of the amygdala in rats by injecting the GABA agonist muscimol. Muscimol injections before training disrupted fear learning in a fear conditioning paradigm. When muscimol was applied after conditioning, but before extinction, the expression of the conditioned behavior (freezing response) was hindered.

The amydala plays a further role in initiating autonomic responses, especially in response to threatening stimuli. An invasive stimulation of the central nucleus of the amygdala of awake rabbits led to several autonomic responses typical for states

of fear or in the presence of threatening stimuli: an increase in respiratory frequency and a decrease in tidal volume, bradycardia, and pupillodilation. The rabbits also discontinued their ongoing behavior (Applegate, 1983). It was concluded that the amygdala takes part in the initiation of species-specific emotional responses towards threatening stimuli.

These studies emphasize the important role of the amygdala in emotional processing. Among these functions are the detection and recognition of salient stimuli, the acquisition and expression of fear, and the initiation of autonomic responses. The amygdala can be regarded as the core structure of the 'fear module'. It responds to the presence of fear-relevant threatening stimuli. By some authors the amygdala is regarded as a salience detector that responds to both negative and positive salient stimuli (Merali, 1998; 2003; Kensinger, 2006). The pattern of activation of different nuclei of the amygdala differs according to the valence of motivation (Knapska, 2006).

2.2.3 Human lesion data

Patients with selective amygdala damage are rare. Urbach-Wiethe is a scarce hereditary disease where normal tissue is replaced by mineral deposits. In one 30-year old woman (S.M.) with a normal IQ, selective damage due to this disease was found in bilateral amygdala. Hippocampus and all neocortical structures were spared. Adolphs et al. (1994) tested this patient in a facial affect discrimination task. Stimuli were facial expressions of the six basic emotions happiness, surprise, fear, anger, disgust, sadness. Three neutral expressions were also included. Faces were depictions of famous persons. The subject had to rate the faces according to several emotional adjectives. Altogether 9 adjectives (happy, sad, disgusted, angry, afraid, surprised, awake, sleepy, interested) were provided and for each picture the subject had to say how well each adjective applied to the expression (scale from 0-5; 0 = not at all, 5 = very much). Two control groups were included, one that consisted of 12 brain-damaged patients with intact amygdala and 7 healthy subjects. S.M. showed a severe impairment in recognizing specifically fearful expressions. The recognition of angry and surprised faces was also impaired but to a lesser extent. In contrast, her ability to identify the persons on the photographs was unimpaired. Controls did not

show any deficits and had high intersubject correlations in their ratings. This study yields support for the hypothesis that the amygdala is necessary to recognize salient emotional cues (in this case seen in affective facial expressions). The fact that particularly the identification of fearful cues was impaired, suggests that this type of stimuli has exceptional salience relative to other emotional facial expressions.

Cahill (1995) demonstrated that the amygdala is also crucial for the memory enhancement of emotionally arousing events. B.P., is a patient with selective bilateral damage to the amygdala complex. When his memory of a narration read to him one week prior to the test, memory disturbances merely occurred for strong emotional, but not for neutral content. This indicates a selective involvement of the amygdala in emotionally salient memories.

Beyond this function of enhancing memory of emotional events, Anderson (2001) found evidence that the amygdala also modulates the perceptual sensitivity to emotionally salient events via its projections to primary and higher-order sensory areas. This is probably achieved by modulating neural firing thresholds of sensory cortex (Morris & Friston, 1998).

Altogether these studies support the view that the amygdala is necessary for the recognition of emotional cues. Furthermore, the amygdala enhances the perceptual sensitivity of sensory processing areas and it plays a crucial role in memorizing emotional events.

2.2.4 Human amygdala activation tracked by functional imaging studies

The general problems of human lesion data are small sample sizes, variability in the lesion size and precise location, as well as the difficulty that compensatory functions may be accomplished by other brain areas. Nevertheless, lesion studies are one unique method of investigating brain functions but they should be complemented by imaging studies with larger sample sizes of homogenuous groups of healthy subjects.

Generally three different kinds of paradigms have been applied in human imaging studies to investigate amygdala function: stimulation with affective material, classical fear conditioning and extinction, and affective startle modulation. Given the relatively small volume of the amygdala and its localization within deeper structures

of the brain, fMRI methodology with its high spatial resolution is preferrably used compared to PET or electro-/magnetoencephalographic techniques. However, one has to be aware of the technical limitations of the fMRI-technique when trying to measure amygdala activity. Attention has to be drawn to the unavoidable presence of susceptibility-induced magnetic field inhomogenities in the proximity of the amygdala. The amygdala is neighboring the air-filled bony cavities at the skull base. These have different magnetic susceptibilities than brain tissue. Small stimulus-correlated head motions for example, that are particularly seen in psychiatric patients, are likely to result in artifactual “amygdala activations”. A reasonably reliable mapping of amygdala activity is only possible when coronal acquisitions and voxel sizes of 4-8 µl or less are employed (for a more detailed discussion of the methodological problems see Merboldt et al., 2001).

Vuilleumier et al. (2001) used event-related fMRI to determine whether the amygdala is selectively activated by fearful as opposed to neutral facial expressions and in particular whether attention modulates the amygdala response. A matching task required the subjects to decide if one of two simultaneously presented stimulus pairs were the same. Stimulus pairs were either neutral pictures of houses, or pairs of fearful or neutral facial expressions. In addition, the location of the target pair was varied within in a four-field spatial arrangement of four empty frames in which the pictures appeared. The target pair could be arranged horizontally or vertically. Independently of the location of the target pair, either the two horizontal or the two vertical frames where highlighted in advance to the picture presentation. Subjects were instructed to attend only to the stimulus pair in the highlighted frames. This design was applied to control for attention. The question was whether processing of fearful faces is dependent on focussed attention to the stimulus or if it can also occur when attention is directed elsewhere. The authors found a preferential left amygdala activation when fearful faces were shown as opposed to neutral ones. In addition, this effect was independent of whether attention was directed to fearful targets or to distractor pictures. These results show the selective activation pattern of the amygdala in the processing of fearful stimuli that is independent of focussed attention, thereby stressing the evolutionary significance of the ‘fear system’. It is important for an organism to be equipped with an automatic danger detection system that notices any potentially harmful stimuli in its environment even when attention is captured by other less salient cues.

In a life-long process of continuous adaptation, learning processes are vital. One simple form of learning is conditioning. Involvement of the amygdala in conditioned fear acquisition and extinction in healthy humans was demonstrated by LaBar et al. (1998) in an echoplanar fMRI study. The authors further found a habituation of amygdala responses across trials in both experimental phases. Activity during acquisition and extinction indicates the involvement in learning and storing associated stimulus-punishment-contingencies. Habituation of neural responses within and across trials may preserves the neuron's capacity to boost its firing rate again when a novel threatening stimulus appears. Neurons that rapidly habituate are concerned with the detection of novel or changing patterns of stimulation. Threat and novelty are linked concepts in the way that novelty (as well as change) are important triggers of fear (Gray, 1987).

Although it is without doubt that the amygdala responds particularly to threatening stimuli, it has already been noted above that some authors found evidence for a more general function of processing different kinds of emotionally salient stimuli. This means that not valence per se might be the essential modulator but the more general concept of salience. The more salient a stimulus is, the more amygdala reactivity is expected. The responsiveness to salient cues of different valence was shown in a fMRI study by Breiter et al. (1996). They also confirmed earlier findings by Bordi et al. (1992, 1993; see below) in demonstrating a rapid habituation to these stimuli. Fearful, happy and neutral faces were briefly (~200ms) presented in a counterbalanced order in a passive viewing task. Bilateral anterior amygdala activation (left > right) was measured in the fearful versus neutral condition. For happy faces a left-sided anterior amygdala activation was found. Neutral facial expressions did not lead to significant activity increases in anterior amygdala relative to a simple fixation point on a plain background. Further analyses over time revealed within and across runs decreases of amygdala activity for fearful and happy faces indicating rapid habituation.

This habituation effect was observed earlier by Bordi et al. (1992) in the lateral amygdaloid nucleus of rats in response to repeated presentations of loud aversive bursts of white noise. A large amount of cells fired only in response to the first two to five noise bursts and remained unresponsive afterwards. Even when long interstimulus intervals of several minutes separated the repeated noise bursts, habituation was observed (Bordi, 1993).

In line with Breiter (1996), Garavan et al. (2001) found selective activity in the amygdala for both positively and negatively valenced stimuli as opposed to neutral, supporting the view of processing the emotional significance of stimuli in general. However is was interesting to see that the arousal level modulated the amygdala response for negative, but not for positive stimuli.

In conclusion, the above imaging studies demonstrate selective activation of the amygdala when a subject is confronted with salient emotional stimuli. This is particularly true for fear relevant material, but an increasing number of studies found similar activation patterns also for appetitive cues. Therefore the amygdala can be regarded as a 'salience processor'.

2.2.5 Major functions of the amygdala – conclusions

The amygdala encodes the emotional meaning of environmental stimuli and mediates emotional learning and memory. It represents the core structure in the brain for the detection of and reaction to potentially threatening, but also emotionally positive stimuli. Its involvement in the acquisition and expression of fear reactivity has been demonstrated in several animal and human studies (Weiskrantz, 1956; Muller, 1997; LaBar, 1998). The amygdala operates in an automatic mode that is independent of focussed attention (Vuilleumier, 2001). It modulates the perceptual sensitivity to salient stimuli (Anderson, 2001). This enables an organism to filter out for example dangerous stimuli by supporting perceptual vigilance under conditions of limited attention. Thereby it elevates the chance that these stimuli reach awareness.
Although salience seems to be the key for activity modulation (Breiter, 1996), the amygdala has been shown to be particularly sensitive to the detection of threatening stimuli (Adolphs, 1994). It is hypothesized that threatening stimuli are especially salient because they are vital for survival. In general the amygdala is responsible for discriminating motivationally relevant stimuli, and for initiating autonomic reactions in response to the appraised stimuli (Applegate, 1983). An important feature of at least a subgroup of amygdala cells is that their activation is characterized by rapid habituation (although not complete) in the persisting presence of the same affective stimuli (LaBar, 1998; Bordi, 1992, 1993). Probably habituation occurs as soon as the affective evaluation of novel stimuli is finished. Long-lasting changes in neural activity

after confrontation with dangerous stimuli indicate emotional learning and memory storage. Temporary functional inactivation of the amygdala or lesions result in difficulties in the expression of formerly learned conditioned fear reactions (Muller, 1997). Amygdala modulation is critical for enhanced memory of emotionally arousing events (Cahill, 1995). Substantial projections to the hippocampus enable the amygdala to influence the memory consolidation of emotionally salient events. As will be seen in the upcoming sections, the amygdala excessively interacts with the orbitofrontal cortex. Whereas the amygdala is responsible for the emotional appraisal of salient stimuli, the orbitofrontal cortex receives a representation of that information that is used for the initiation of goal-directed behavior.

2.3 Involvement of the orbitofrontal cortex

2.3.1 General function of the orbital region of the frontal cortex

Although the amygdala represents the core structure in the appraisal of the emotional salience of a stimulus, other brain areas also share the important function of representing the emotional value of sensory stimuli. The frontal cortex has been found to differentially process affective material (e.g. Northoff, 2000; Blair, 1999). In general, salient negative or positive events are transformed into action by distinct frontal networks (Damasio, 1995). An organism has to respond and adjust to rewarding and punishing stimuli in the external and internal environment. Emotions can be regarded as 'motive states' elicited by these kinds of stimuli (e.g. Rolls, 1995) that initiate behavioral alterations. The orbitofrontal cortex (OFC) regulates behavior in dependence of the rewarding or punishing value of a stimulus, thus being crucial for motivated behavior. The OFC encodes the motivational importance of stimuli and determines the specific target-oriented behavior (Tremblay, 1999). In the presence of a threatening stimulus it might be important to suppress the current behavior and to initiate appropriate behavior. In addition, the OFC is involved in learning new stimulus-reward/punishment-contigencies and it keeps a memory of once learned associations to react more quickly and adequately in an upcoming similar situation (Tremblay & Schultz, 2000). For these functions representations of the emotional significance of stimuli and of ongoing events are crucial. This information is provided

by the amygdala that has direct reciprocal connections with the OFC (Krettek, 1977; McDonald, 1991). Information about the emotional valence is transferred to the OFC, which leads to differential activity in this region. An overview of supportive evidence from imaging studies for the general contribution of the medial prefrontal cortex to emotional processing can be found in Phan (2002).

2.3.2 Differential activity in the orbitofrontal cortex as a function of the emotional salience of facial expressions

Imaging studies have documented the differential responses of the OFC in association with the emotional significance of a stimulus as a signal for target-oriented behavior. The majority of investigations comes from the field of facial affect discrimination.

Hornak et al. (1996) investigated the performance of a group of patients with OFC damage, using a task in which subjects had to identify facial and vocal emotional expressions. Patients suffered from right or bilateral damage to the ventral frontal cortex due to closed head injury or stroke. In a first task, subjects were presented with photographs of emotional facial expressions and were asked to screen a list for the adjective that best described the depicted affect. In order to control for mere perceptual difficulties, a simple face recognition task was included. Further, a vocal expression identification task was performed in which subjects had to label non-verbal emotionally modulated sounds (for example crying, moaning). As a control for perceptual problems, an emotion-free voice discrimination test was included and an environmental sounds test, in which patients had to name neutral sounds like water dripping. In addition, self-ratings of the subjective change in one's ability to experience different emotions (sadness, anger, fear, disgust, enjoyment) were assessed. Furthermore, behavioral changes were journalized by hospital staff. Patients were relatively unimpaired in the two perceptual control tasks. Severe deficits were seen in both the emotional face and voice expression identification tests. This suggests a double dissociation and demonstrates that impairments are specifically related to emotion processing. Further, these patients reported a reduction of the ability to feel one or more of the alleged negative emotions. This was particularly striking for fear. Some patients reported even a complete absence of fear

since the injury. Moreover, patients lost their ability to feel empathetic with the sufferings of others. In addition, many subjects reported some reduction in positive emotion. Behavioral ratings by the hospital staff indicated higher levels of impulsiveness or aggression, disinhibited or socially inappropriate behavior, misinterpretation of other people's mood and lack of initiative. A control group with damage to the brain outside the ventral frontal areas did not show the named deficits nor the named changes in subjective emotional experience and behavior. The described study outlines the diverse behavioral problems of patients with damage to the OFC. These can be regarded as a result of an inability to choose an adequate behavioral responses to salient stimuli. Further, emotional cues are no longer adequately interpreted. The OFC contributes to these tasks in healthy subjects.

The involvement of the OFC in emotional processing is supported further by the findings of Vuilleumier (2001), who found selective activation of the right lateral OFC while subjects watched pictures of fearful facial expressions. This activation was not found when neutral slides were presented.

Not only fearful faces, but also angry ones are a potential signal of danger. Angry facial expression may signal that an opponent wants to harm the observer. Blair et al. (1999) investigated the role of the OFC in processing angry and sad faces using PET. Stimuli were photographs of males and females from the Ekman (1978) set that were graphically manipulated to create a set of pictures varying in the intensity of the anger expression. Subjects were engaged with a sex discrimination task and were not aware that the implicit emotional factor was crucial. PET analyses revealed significant activation in the right orbitofrontal and bilateral anterior cingulate cortex. Furthermore, with increasing intensity of the anger expression the activity was likewise augmented. The latter finding is particularly important since it stresses that the more intense or salient a stimulus is, the stronger is the orbitofrontal response.

The documented studies revealed severe impairments in emotional discrimination tasks in patients with damage to the OFC. These patients are also characterized by severe behavioral problems because emotional stimuli are not adequately interpreted. Furthermore, the OFC has been shown to be activated in emotional processing. The more intense an emotional stimulus, the stronger is the neural OFC response.

2.3.3 Differential activity in the OFC in response to a range of emotional cues

The above studies used affective facial expressions as stimuli. It is well known that faces are processed by specialized neurons in different brain areas including the frontal cortex (e.g. Scalaidhe, 1999). Hence, it seems conceivable that the effects reported above are partly due to the outstanding characteristics of facial stimuli. To counteract this objection, studies are reported in the following that used picture sets of more general and to a great extent 'face-free' emotional depictions with high motivational relevance.

An animal study with rats (Schoenbaum, 1998) provides evidence that the OFC responds to behaviorally significant stimuli of both, negative and positive valence. In a go/no-go odor discrimination task, rats learned an adaptive behavioral strategy of responding to an odor that predicted a rewarding outcome and of withholding the response when an odor signalled an aversive outcome. Activity in OFC and basolateral amygdala was measured in the learning phase of the task before the rats reached the behavioral criterion. The recording period was a short variable delay interval between the offset of the respective odor and the onset of delivery of the rewarding/punishing outcome (either a tasteful or an aversive fluid). The activity in the amygdala and OFC during both rewarding and punishing trials increased relative to the pre-trial baseline. In addition, a differential neural response depending on the outcome was seen in both structures. A substantial population of cells fired significantly more often in the aversive than in the rewarding go trials. This differential neural response occurred although the rats had not yet learned the adaptive behavioral odor discrimination. This means that neurons had acquired a discriminatory ability in advance of behavioral adaptation. The activity of cells in the OFC and the amygdala was modulated by the anticipation of either positive or negative consequences. Further, it was found that the relative neural response selectivity increased significantly as rats became more confident in their behavioral discrimination across acquisitions. Thus, elevated activity in the OFC is determined by a subject's expectancy for reward or punishment. The OFC and the amygdala are strongly involved in the regulation of adaptive goal-directed behavior. Both structures form a functional cooperation with distinguishable specialized assignments.

The speed of the orbitofrontal response to aversive stimuli was demonstrated by Kawasaki and colleagues (2001). They recorded single-neuron responses to

affective slides taken from the IAPS and to different emotional facial expressions taken from the standardized Pictures of Facial Affect (Ekman, 1976). The subject was an otherwise healthy patient who had a history of epilepsy and underwent neurosurgical intervention. Depth electrodes were implanted in ventral and medial prefrontal cortex to record the neural firing rates while the patient watched the affective stimuli. In response to aversive stimuli an initial short-latency transient inhibition of the firing rate was replaced quickly by a prolonged excitation in the medial areas of prefrontal cortex. For neutral stimuli firing rates stayed the same pre and post stimulus presentation. The differential responses to aversive material became significant as soon as 120ms after stimulus onset. It was hypothesized that the observed responses may indicate increased emotional arousal elicited by stimuli signalling threat or danger.

Whereas most studies investigated orbitofrontal function with PET or fMRI, few employed MEG as a functional measure. In a combined fMRI/MEG study, Northoff et al. (2000) demonstrated a functional dissociation between medial orbitofrontal and lateral prefrontal activation in response to stimuli of different valence. In an emotional-motor stimulation, subjects viewed positive, negative, and neutral pictures from the IAPS and they had to press a button as soon as a new picture appeared. fMRI measurements registered increased medial orbitofrontal activation only when negative pictures were shown. In addition, a significant negative correlation was found between activity in medial orbitofrontal and lateral prefrontal cortex. In contrast, lateral prefrontal activity that was negatively correlated with activity in orbitofrontal cortex, emerged in response to positive slides. Neutral pictures did not change activity in these two regions. MEG analyses were in line with this differential activity pattern: equivalent current dipoles of the early magnetic field were localized in medial and anterior orbitofrontal cortex for the negative and in either lateral orbitofrontal or lower lateral prefrontal cortex for the positive images. The non-emotional neutral condition did not produce early orbitofrontal dipoles. Further, dipole onset was significantly earlier for the negative compared to the positive pictures. No lateralized effects were found. The differential activity pattern observed in response to negative and positive emotion processing points towards a functional dissociation of medial and lateral orbitofrontal regions. It may be argued that the anterior/medial region is functionally involved in negative emotional processing while the lateral region may

serve the function of forming associations between emotions and thoughts (Drevets, 1998).

These findings can be explained by cytoarchitectonic and connectional differences between the two regions: the medial orbitofrontal cortex bears an agranular or dysgranular structure and has connections to the hippocampus, ventrolateral parts of the basal nucleus of the amygdala, dorsolateral prefrontal cortex, dorsomedial parts of mediodorsal thalamic nucleus and anterior cingulum. On the other hand the lateral orbitofrontal cortex features a granular cytoarchitecture and holds connections to the ento-/perirhinal cortex, ventromedial parts of the basal nucleus of the amygdala, dorsolateral prefrontal cortex, ventromedial parts of the mediodorsal thalamis nucleus, premotor cortex, parietal cortex and posterior cingulum (Morecraft, 1992; Carmichael, 1996).

The outlined studies provide clear evidence for OFC activity in response to a variety of different aversive and appetitive visual stimuli. Emotional arousal seems to mediate this activation. The OFC integrates and organizes information and selects an adequate behavior that depends on the expected punishing or rewarding consequences of a stimulus.

2.3.4 Conclusions

In conclusion, OFC activation follows the perception of evocative stimuli that are subjectively relevant for operant goal-directed behavior (Vuilleumier, 2001; Schoenbaum, 1998). After learning that certain stimuli are associated with reward or punishment , the OFC initiates behavioral alterations whenever the stimulus is present, to cope with it and to adapt to the environment. Stimuli differ in their behavioral significance that depends on their potential consequences. A strongly aversive stimulus that signals severe threat or harm elicits pronounced orbitofrontal activation. With increasing intensity of the threatening stimulus the orbitofrontal areas respond with a proportional augmentation of activity (Blair, 1999). Although activity in OFC can be elicited by any emotionally significant stimulus, anterior and medial areas are particularly specialized for the processing of aversive cues (Northoff, 2000). Patients with damage of the OFC report a diminished or even complete absence of the subjective perception of fear (Hornak, 1996). The OFC has extensive

connections with the amygdala (McDonald, 1991). Both structures form a functional unit and are part of a brainstem-amygdala-cortical alarm system that reacts differentially and rapidly to stimuli signalling potential threat to the self (Kawasaki, 2001). The OFC keeps a memory of formerly learned stimulus-reward/punishment-contingencies in the process of environmental adaptation (Tremblay & Schultz, 2000). This enables an organism to react quickly and adequately in dangerous or threatening situations.

2.4 Amygdala – frontal interactions

Behavior is guided by expectancies of its possible outcomes. Throughout life an organism learns and makes experiences with stimuli and actions. Some of these stimuli and actions predict or lead to desirable, some to aversive outcomes. Once the organism has generated associations between stimuli / responses and their reinforcing consequences in memory, these associations allow access to representations of future events. This anticipation of future events on the basis of activation of formerly learned reinforcer representations by predictor stimuli (conditioned stimuli) is called ‘expectancy’. The functional unit of amygdala and OFC plays a key role in forming and use of the expectancies of reinforcers (Holland, 2004). These expectancies guide goal-directed behavior.

An experimental design to investigate reward expectancy is reinforcer devaluation (Rescorla, 1987). An animal learns an instrumental discrimination task in which two different operant behaviors lead to two different rewarding outcomes (for example two different food rewards). Later the value of one reinforcer is changed by allowing access until satiation. The animal will subsequently reduce the operant behavior that predicts the devalued reinforcer relative to the unaffected one in an extinction trial. The involvement of amygdala and OFC in these processes is demonstrated by the fact that either lesions (Malkova, 1997) of the amygdala or disconnection (Baxter, 2000) of the two areas extinguish the devaluation effects.

Further, human brain imaging studies showed a reduction of activity in the amygdala and OFC when a reinforcing stimulus has been devalued (Gottfried, 2003). In tasks of reversal learning, whenever reinforcer contingencies were altered,

neurons in the amygdala and OFC that fired selectively to the delivery of the reinforcers, respectively changed their coding properties (Schoenbaum, 1999).

Amydgala and OFC have specialized functions in the formation and use of reward expectancies. The formation of stimulus-reinforcer expectancies seems to be achieved by the amygdala, whereas the OFC is involved in the generation of responses on the basis of these expectancies. This hypothesis is supported by Pickens (2003), who examined rats with lesions to the amygdala or OFC in different stages in a devaluation experiment. Rats learned to associate a light with the delivery of food. Later a taste aversion protocol was introduced, in which animals received a substance together with the food, that induced sickness. After this, the devaluation test was performed and the animals' food approaching behavior in response to the light cue was measured. When lesions to the amygdala were made before the light-food conditioning phase, the rats' performance in the food devaluation task was impaired. This was not the case when lesions were made after the conditioning training. It is assumed that the light cue was already associated with the motivational properties of the food reinforcer and that this association was represented in other brain areas (e.g. OFC). In contrast, OFC lesions had detrimental effects on the devaluation task regardless of whether the lesions were made before or after the conditioning phase. Thus, the OFC seems to keep a record of the stimulus-reinforcer contingency that is used for goal-directed behavior. The OFC is thereby responsible for the generation of responses, whereas the amygdala is crucial for the forming of this stimulus-reinforcer association.

Although the importance of the amygdala in the long-term use of stimulus-reinforcer association beyond of their initial formation is verified (Schoenbaum, 1998; LeDoux, 2000) it seems that in some aspects there are sufficient substrates of that learning elsewhere in the brain (e.g. OFC) that can compensate for damage to the amygdala.

In summary the amygdala is essential for the initial stimulus-reinforcer acquisition and the OFC keeps a representation of this association and further uses this 'outcome expectancy' for the guidance of behavior. This is in line with the results of a human imaging study (Gottfried, 2002), in which amygdala activity was recorded during an appetitive conditioning phase, together with additional activity in the OFC. Whereas amygdala activity habituated, indicating that the stimulus-reward contingency had been established, activity in the OFC remained.

Thus, the interaction of amygdala and OFC seems essential for acquiring and employing expectancies of the motivational value of upcoming stimuli or events. These expectancies are used by the OFC for the adaptive guidance of goal-directed behavior.

2.5 The brainstem-amygdala-cortical alarm system in PTSD

PTSD is increasingly described as a disorder related to memory. Core symptoms are intrusive thoughts or reexperiencing of the trauma, avoidance of reminders, and generalized hyper-arousal (American Psychiatric Association, 1994). Reexperiencing is the most prominent symptom and can be triggered by external environmental cues that remind the patient of his traumatic events. Through the process of fear conditioning, formerly neutral or insignificant stimuli become fearful or significant once after the trauma. As outlined above, the amygdala is strongly involved in fear conditioning. Imaging studies have shown activation of the amygdala complex in a range of fear conditioning paradigms. Yet, one constraint of most fear conditioning studies is the use of rather simple stimuli as unconditioned stimuli (US) (for example electric shock, loud noise, or non-moving aversive pictures). The events that induce PTSD on the other hand are often far more complex. Hence, the question arises, whether the amygdala would show similar responses in more complex settings of fear conditioning. Doronbekov et al. (2005) tried to simulate the changes of the emotional significance of formerly neutral stimuli through fear conditioning by employing complex and more realistic video clips of extremely fearful content. The conditioned stimuli (CS) were emotionally neutral pictures of trees etc.. The aversive video clips always contained images similar to the content of the CS-pictures (in this example trees) and in addition an aversive element was introduced (for example man killed and eaten by tribe of cannibals in the forest). In a first phase neutral photos were shown to 10 healthy subjects and rCBF was measured. In the second phase the fearful video clips were shown. In the test phase the same photos of phase one were shown again, accompanied by rCBF measurements. As a control condition, neutral photo-neutral video clip pairs were used that did not induce any emotions. Results revealed that 5 of the 10 subjects showed successful fear conditioning. They reported that after the video clips, the neutral photo became more fearful. In these

subjects rCBF increases in the amygdala to the now fearful photos were registered in the test phase. A lack of amygdala activity was reported in the control condition. Further, the subjects that did not show fear conditioning neither showed amygdala activity regardless of the experimental condition. This study demonstrates that originally neutral stimuli activate the amygdala whenever they become associated with complex fearful events. The complex fearful video clips used are more representative of the traumatic events that induce PTSD than the simple stimuli employed in most experiments.

It has been outlined above that amygdala recruitment takes place in an automatic manner when subjects passively watch emotionally salient stimuli. Further, it is well known that healthy subjects show a stronger amygdala activity in response to fearful versus happy facial expressions (Breiter, 1996). This activation is automatic and takes place without conscious awareness as demonstrated in backward masking paradigms (Morris, 1998). It was hypothesized that PTSD patients suffer from a hyperresponsive amygdala that strongly responds to general threat-related stimuli. In order to test this hypothesis, Rauch et al. (2000) compared amygdala activation in combat-exposed Vietnam veterans with and without PTSD in a backward masking paradigm. Stimuli were fearful, happy, and neutral facial expressions. Presentation time of each picture was 33ms, followed by a 167ms presentation of a neutral mask. In both groups fMRI analyses showed higher amygdala activity in response to fearful as compared to happy and neutral pictures. The PTSD group exhibited significantly greater amygdala responses to negative slides than the control group. 75% of the PTSD patients exceeded the highest mean value in the non-PTSD group. Correlative analyses revealed a significant positive correlation between fMRI signal intensity change within the amygdala and the severity of PTSD symptoms. No correlations were found with comorbid depressive symptoms, stressing the specificity of the results for PTSD. The described findings confirm the hypothesis of a hyperresponsive amygdala in PTSD and its strong activation in the unconscious processing of fearful stimuli. The masked presentation prevented conscious perception of the pictures. Thus, hyperresponsiveness refers not only to explicitly trauma-related stimuli but to general threat-related cues. Moreover, there seems to be a linear relationship between the strength of amygdala activity and the PTSD symptom severity. The lack of correlation with depressive symptoms is important in marking the specificity of exaggerated amygdala responses in PTSD. Depression is a

frequent comorbid disorder in PTSD, but does not seem to contribute to the observed findings.

Several other symptom provocation studies support and extend the abnormally strong amygdala response to threatening stimuli in PTSD. Pissiota et al. (2002) found an increased rCBF in the amygdala when PTSD patients were exposed to trauma-related compared to neutral sounds. rCBF increases were positively correlated with self-reported anxiety. Autonomic arousal was also higher in response to aversive sounds. In contrast to the study by Rauch (2000, see above), who investigated vietnam veterans whose traumatic events dated back more than 30 years, Pissiota examined subjects with PTSD resulting from more recent (traumatic events dated back approximately 7 years) wars. PTSD was either combat- or torture-related.

Liberzon (1999) confirmed amygdala involvement in response to combat-related sounds as opposed to white noise in PTSD subjects. A combat-exposed non-PTSD and a healthy control group did not show a significant activity increase in the amygdala.

Similar activity patterns were found for the OFC in a script-driven emotional imagery experiment by Shin et al. (1999). A group of female subjects exposed to childhood sexual abuse was investigated with PET. Half of the subjects had a diagnosis of PTSD. Each subject provided descriptions of two individual autobiographical neutral and two negative abuse-related scripts respectively. These scripts were read to them during measurement of rCBF. Subjects were instructed to vividly recall and imagine the read events. Results showed for both groups significant activity increases in orbitofrontal and anterior temporal areas in the negative relative to the neutral imagery condition. A significant group x condition interaction revealed stronger activity increases in the PTSD group than the comparison group. PTSD subjects were characterized by greater heart rate responses and higher blood pressure. Although these findings suggest that salient stimuli (as opposed to neutral) result in stronger orbitofrontal involvement irrespective of a PTSD diagnosis, the hypothesis of hyperresponsiveness to threatening stimuli in PTSD is supported. The neural responses to fearful stimuli are always significantly stronger in PTSD patients compared to non-PTSD subjects. The study extends the findings of a hyperresponsive amygdala to OFC.

Further support for the enhanced activation of OFC in the context of traumatic stimuli comes from a study by Driessen et al. (2004). Patients with Borderline personality disorder and a history of traumatization were investigated with fMRI during the recall of either personal traumatic episodes or personal negative but non-traumatic episodes. Half of the subjects had a current PTSD. Contrasting the traumatic and the non-traumatic conditions for the complete subject sample, a stronger activation of OFC was registered in the traumatic condition.

The findings of hypersensitive responses of amygdala and OFC to threatening stimuli in PTSD parallel results from studies investigating peripheral physiology in PTSD (e.g. Orr, 1998; Pitman, 1987). In those studies the exaggerated peripheral responsiveness to dangerous stimuli in PTSD was likewise established.

Altogether a decreased threshold for amygdala and OFC activation in response to fear-related material has been demonstrated in PTSD patients. Both, the amygdala and the OFC seem to be hyperresponsive in PTSD. These two structures show abnormally strong activity in response to consciously or unconsciously perceived threat-stimuli, and stronger autonomic responses are initiated.

2.6 Summary and hypotheses for the present study

Evidence was reported for a fast and rapidly acting brainstem-amygdala-cortical alarm system. This system operates automatically and independent of conscious awareness or attention. The amygdala is responsible for the emotional tagging of a stimulus. Prior experiences with the same or a similar stimulus establish stimulus-reward/punishment contingencies. These are activated in case of further exposures to the stimulus. Thereby these stimuli are processed faster. A copy of the stimulus-reinforcer association is transferred to the OFC. In the OFC this information constitutes an outcome expectancy that guides goal-directed behavior. In PTSD this alarm system is hyperresponsive. Exaggerated amygdala and OFC activation in response to threatening stimuli is confirmed by various studies, involving trauma-related stimuli but also a large variety of unspecific threatening or fearful cues. Those stimuli are most salient for the patients since in the past (and presence) they signalled danger to ones life or bodily integrity.

The exact rapidity of this alarm systems in PTSD has not been investigated. There is only one study to date that provides clues: Junghoefer et al. (2003) found an early emotional modulation in frontocentral and orbitofrontal regions. Thirteen torture victims with a current diagnosis of PTSD and a matched healthy control group were shown aversive and neutral pictures from the IAPS. Pictures were presented in an alternating order with a stimulus duration of 333ms and no interstimulus interval. Subjects passively viewed the pictures while MEG-recordings were done. It was found that negative pictures in general produced stronger frontal activations than neutral ones in both groups. The most interesting result though was the observation that PTSD patients had significantly stronger activations in frontocentral and orbitofrontal regions in response to the negative pictures as compared to the controls. Group differences were strongest in an early time interval from 60-110ms (see Figure 3). The authors reasoned that a lack of (medial) prefrontal cortex regulation of the fear network may be responsible for the hyperresponsiveness. As outlined above, the fear network involves the interaction between amygdala and OFC.

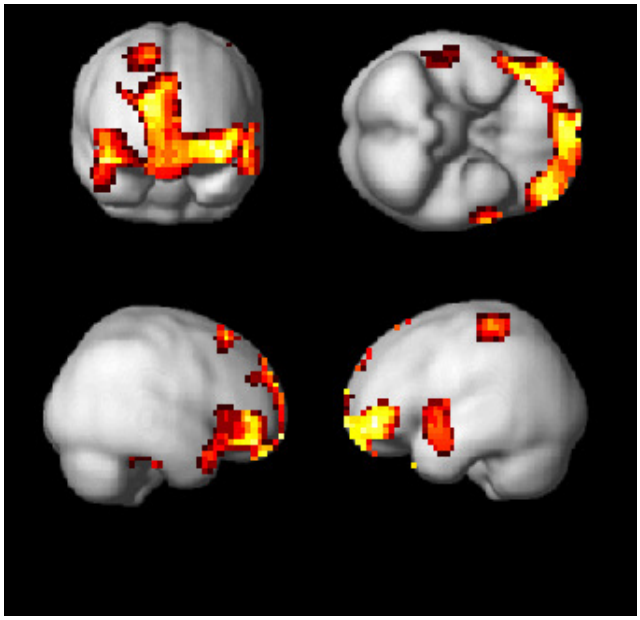


Figure 3: Areas of significant group effects in the 60-110ms interval in the Junghoefer study (2003). PTSD subjects had a significantly stronger activation in frontocentral and orbitofrontal regions when viewing aversive pictures compared to the control group (Figure provided by Markus Junghoefer).

The present study aimed for the replication of the finding of cortical indices of an early enhanced threat detection system in PTSD. It should further test the hypothesis of an exaggerated threat detection system in a design using longer stimulus presentations and interstimulus intervals. In the Junghoefer study Rapid Serial Visual Presentation (RSVP) was used with a stimulus duration of 333ms and no interstimulus interval. According to Potter (1976), the immediate succession of pictures in the RSVP paradigm can interfere with the further processing of the pictures. The main focus of the present study was to assess the temporal onset of exaggerated fear-network responsivity in PTSD. The brain area of interest was the OFC. The OFC keeps a record of the amygdala's emotional appraisal and forms an outcome expectancy that guides goal-directed behavior. Since threatening stimuli are most salient for PTSD patients, we expected an early differential OFC activity in response to stimuli of varying valence (negative, positive, neutral). It was hypothesized that PTSD patients show stronger activity in the OFC in response to negative as opposed to positive and neutral pictures. The activation in response to negative pictures was expected to be highest in the PTSD group as compared to the three control groups. Due to the suggested hyper-responsiveness of the fear system in PTSD, this early affective modulation should be significantly weaker in control subjects.

Magnetoencephalography (MEG) was chosen to investigate the exact onset and time course of emotional modulation in the OFC. The advantage of whole-head MEG is its high temporal resolution (< 1ms) that makes it possible to record dynamic cortical processes.

3 Repetition suppression: a by-product of an automatic sharpening mechanism for threat stimuli in visual priming

One particular neuronal effect is commonly observed in memory-demanding tasks like delayed matching-to-sample tasks. This effect is 'repetition suppression' (e.g. Desimone, 1996). Repetition suppression refers to a decline of neuronal responses that occurs with repeated exposure to the same visual stimulus. This effect occurs in different cortical cell populations in frontal, temporal, and occipital regions, as well as in the amygdala (Ishai, 2004). Miller (1994) notes that the suppressive effect is automatic and does not require active engagement of working memory. Repetition suppression may underlie perceptual priming, which is a nonconscious or implicit form of memory (Wiggs, 1998). The suppression effect seems to be an automatic, intrinsic response of cortical neurons. Evidence for this hypothesis comes from studies showing the effect under anesthesia (Miller, 1991) and cholinergic blockade (Miller, 1993). However, more rencent studies foster the view that top-down influences on sensory processing play a crucial role (e.g. Ergenzinger, 1998). For the somatosensory system for example it has been shown that descending projections from the primary somatosensory cortex to the thalamus are seven to ten times greater than the ascending projections (Liu, 1995). Such top-down projections strongly modulate sensory processing. Further, the following features characterize repetition suppression: it can occur even in cases when many intervening stimuli lie between the first presentation and later repetition of a stimulus (Li, 1993). Preserved suppressive effects have been observed after delays of hours (Fahy, 1993). Its strength correlates positively with the number of repetitions and its onset can be very early after the onset of the repeated stimulus (Li, 1993). Importantly, repetition suppression is modulated by emotion (Ishai, 2004). According to Desimone (1996) repetition suppression is a by-product of a cortical sharpening mechanism. With repeated stimulus experience, neurons that code features of the stimulus that are essential for its recognition, keep showing a robust response. Contrary, neurons that represent stimulus features that are not crucial for identification, decrease their activity or are inhibited. As a result, connections between suppressed and still active neurons are weakened. Thereby the cell ensemble or network becomes 'thinned out' and more selective. It might be argued that this represents some form of noise filtering. A behavioral consequence is a more efficient and faster object identification.

Further, due to the reduced overall activity the processing resources are freed for other stimuli. A schematic model of this effect is shown in Figure 4 (taken from Wiggs, 1998). The repetition suppression effect will be outlined in more detail in the following sections. It might be argued that anxious subjects, like PTSD patients, are characterized by decreased repetition suppression in response to repeated exposure to threatening stimuli. The present study sought to investigate this question.

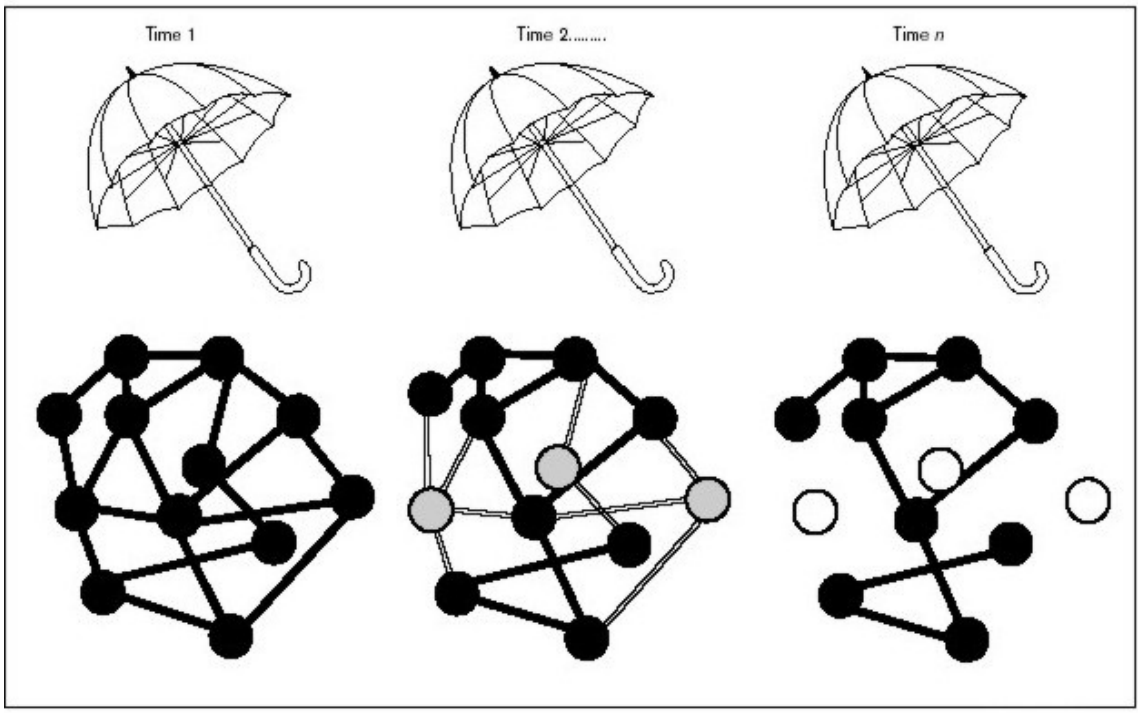


Figure 4: The neuronal network representing a visual stimulus changes with repeated exposure to this stimulus. At the time of the initial perception (left), a large interconnected cell ensemble is active. Simplified, each neuron represents one specific feature of the object. With repeated experience with the stimulus, neurons that represent features not essential for object identification drop out of the pool of active neurons by showing response suppression (middle). Top-down inhibitory effects may play an important role in the generation of this effect. As a consequence, connections with the still active neurons that encode crucial object features are weakened (right). This sharpening mechanism with associated repetition suppression results in faster and more efficient object identification (Figure taken from Wiggs et al., 1998).

3.1 Brain areas showing repetition suppression

3.1.1 Single-cell recordings in the temporal cortex of monkeys

Brown et al. (1987) and Baylis and Rolls (1987) were the first to explore repetition suppression. Both groups recorded neuronal responses of single cells in the temporal cortex of monkeys in a recognition memory task. Brown et al. measured neuronal firing of inferomedial temporal areas during a delayed matching task. Monkeys were successively presented two visual stimuli that could either be different or identical. The monkeys should decide via button press if the two stimuli were the same. A reward was given for correct responses. Between the depictions of the two target stimuli, intervening distractor objects were presented. The number of intervening items varied over trials and lay between 0 and 15. This resulted in a maximum delay between the two target stimuli of up to 100s. The authors registered a significant activity decrement in the cortex upon repetition of the stimuli. This was independent of the duration of the delay period and independent of the number of intervening distractors. This habituation-like effect was concluded to reflect some sort of memory for the previous occurrence of visual stimuli. Neuronal recordings from the hippocampus and subicular cortex were not characterized by this repetition suppression.

Baylis and Rolls (1987) extended these results by showing the same effect in neurons located in the inferior temporal and the adjacent cortex in the anterior part of the superior temporal sulcus of rhesus monkeys. In their delayed matching to sample task delays of 2 to 5s separated the first and second presentation of either the same or different visual stimuli. The majority of neurons showed lower response rates to ‘familiar’ stimuli.

These findings are in line with the report that cooling of the inferior temporal gyrus produces impaired performance in delayed matching to sample tasks (Horel, 1982).

An overview of single-cell recording studies in monkeys can be found in Ringo (1996). The author concludes hat repetition suppression is generally found to be strongest in the anterior inferior temporal gyrus. Further, he states that neurons with strong repetition suppression can show an activity reduction of over 50%, although some cells ‘fall asleep’ completely at the occurrence of the first stimulus repetition.

Thereby the stimulus specificity of the neurons is stressed. The recorded neurons adapt or show suppressed activity only to repeated items. No generally reduced response rates are found. Neurons show unaltered response rates to non-repeated intervening stimuli. It was further hypothesized that a depression of synaptic effectiveness between neurons takes place.

3.1.2 Single-cell recordings in human temporal cortex

Analogous invasive single-unit recordings in humans are scarce. In a slightly different paradigm, Haglund et al. (1994) recorded neuronal activity extracellularly from the lateral cortex of the left anterior temporal lobe in patients undergoing epileptic surgery. Subjects viewed a target slide depicting an object (for example a cake or a broom). This object should be retained in memory. It was followed by three distractor slides, two of them showing different objects, one showing a blank slide. Subjects were instructed to name all objects at the time of appearance. Each slide was presented for 4s. After the presentation of the distractors, subjects were requested to recall aloud the name of the target object. Following the recall, a new sequence of three distractors was shown, followed again by the request to name the target. A third distractor / recall sequence was finally added resulting in a total of three serial retrievals. Therefore, ‘re-presentation’ or repetition of the target object was not by its successive repeated depiction (like in the animal studies), but rather via a recall instruction. A decreasing neuronal activity from the first to the third retrieval was observed for a significant proportion of recorded cell populations. It was noted that this fading of neuronal activity is progressive in the way that a continuous activity decline was recorded over the three retrievals.

3.1.3 ERP findings of repetition suppression in temporal cortex

In further agreement with the above studies, Begleiter et al. (1993) found repetition suppression in temporal brain areas in a group of healthy human volunteers. In an event-related potentials (ERP) study, 25 healthy participants had to perform a delayed matching to sample task. Stimuli were line elements that were difficult to

name. These were chosen to exclude possible semantic influences on the involved mnemonic processes. In half of the trials an identical test stimulus followed the target stimulus after a fixed inter-stimulus interval of 1.5s. In the remaining trials a different test stimulus was shown. Via button press, subjects had to indicate whether the training and test stimuli were the same. Performance reached an accuracy level of far over 90% for all subjects. Several peaks were found in the ERP signal. One peak reached its maximum amplitude at around 240ms (P240) and had a significantly smaller amplitude to matching stimuli. For non-matching test stimuli an amplitude increase was observed when compared to the sample stimulus. Further, the authors assessed the contributions of various brain regions. It was found that the P240 amplitude reduction was significant only in the temporal region. When current density maps for the P240 were calculated, a strong positive source was found in the right temporal region. The results did not change when the inter-stimulus interval was extended to 4s. It was concluded that the ERPs to the test stimulus reflect information about the memory of the preceding stimulus. The right-sided dominance of the effect is congruent with the fact that right temporal lobe activity is related to memory for visuo-spatial material, whereas the left side is specialized for memory for verbal material (e.g. Milner, 1971). The authors argue in terms of neural network models of memory (McClelland, 1986). Namely that the forming of a memory trace of a visual stimulus is related to modifications of the set of synaptic weights in the neuronal network. The smaller the number of neural elements necessary to represent a stimulus, the more efficient is its processing. The demonstrated repetition suppression in the temporal lobe is the observable manifestation of this mechanism. The hypothesis of a more efficient processing of a familiar stimulus by repetition suppression is further supported by shorter reaction times to matching versus non-matching stimuli.

3.1.4 Repetition suppression in prefrontal cortex of monkeys

Miller et al. (1996) demonstrated that repetition suppression also occurs in neurons of the prefrontal cortex. Single unit recordings were done on a range of prefrontal neurons of macaque monkeys. Complex visual stimuli (digitized colored images from magazines) were used in a special version of the delayed matching to sample task

that was named ‘ABBA’ task. Each trial started with a sample stimulus, followed by zero to four intervening test items that were presented before the final matching stimulus was shown. Stimulus duration was 500ms and the interstimulus interval was 1s. The specific characteristic of the ABBA task is that one of the non-matching intervening pictures is repeated once in the sequence. For example a trial starts with stimulus ‘A’ and is followed by ‘B...B...C...A’. For a correct response the monkeys were rewarded with fruit juice. The investigators found that 78% of recorded neurons were visually responsive and the majority also showed stimulus specificity. About 40% of these cells were characterized by repetition suppression. The number of intervening items had no significant influence on the strength of this effect. Repetition suppression was found not only for the final match stimulus, but also for the behaviorally irrelevant repeated non-match stimuli (e.g. the second presentation of ‘B’ in the above example). This indicates that repetition suppression is an automatic process that occurs whenever a simple stimulus repetition is detected. The authors further compared their results for prefrontal neurons with the findings from an earlier study. This earlier study (Miller, 1994) employed the same method but tested neurons in the anterior part of the ventral inferior temporal cortex. The incidence and strength of the repetition suppression effect were similar in both areas. As outlined for example by Ungerleider et al. (1989), prefrontal and inferior temporal cortex are strongly interconnected.

3.1.5 Repetition suppression in prefrontal cortex of humans

Support for the occurrence of repetition suppression in prefrontal cortex of humans comes from Buckner et al. (1998). In a rapid presentation event-related fMRI study, 20 healthy volunteers performed an object classification task. Prior to the fMRI recordings, subjects were familiarized with a number of colored object slides. In the fMRI runs, trials with novel and familiar object slides were presented in a pseudorandomly intermixed order. Subjects had to perform an object classification task. As compared to novel items, fMRI results revealed significantly weaker activation in response to familiar objects in bilateral extrastriate visual cortex extending into inferior temporal areas, and also left prefrontal cortex, and anterior cingulate. These areas can be regarded as representing the mid-levels of the

processing hierarchy. Brain areas involved in earlier (occipital pole) and later (motor cortex responsible for response output) information processing stages did not show repetition suppression. The authors hypothesized that the decreased activity in temporal cortex represents facilitation of perceptual processes and that prefrontal decreases may be related to the facilitation of conceptual processes.

In a more recent study (Ishai, 2004) the occurrence of repetition suppression in the frontal cortex of humans was also confirmed. In a face working memory task, in which subjects had to detect repetitions of facial expression slides, decreases of neural responses were found in the inferior frontal gyrus across repetitions.

3.1.6 Conclusions about the particular brain areas showing repetition suppression

The outlined studies demonstrate that repetition suppression is an automatic (Miller, 1996) phenomenon of neural networks particularly in the inferior temporal cortex (Begleiter, 1993; Ringo, 1996) and areas of the prefrontal cortex (Miller, 1996; Buckner, 1998). Whenever a stimulus is repeated, activity in a majority of neurons in these cortical areas is decreased. It can be detected with a range of methods including single-unit recordings, ERP-approaches, and fMRI in a variety of different experimental tasks. All of them have in common the repetition of a formerly novel stimulus. The respective brain areas represent the mid-levels of the stimulus processing hierarchy. Repetition suppression has been observed for a variety of different visual stimulus classes including objects, words, and faces (Haglund, 1994; Ishai, 2004). The majority of the involved neurons are characterized by stimulus specificity. The above studies demonstrated that the effect can span several intervening stimuli with delays between target and match of over 100s in tasks like serial recognition (Brown, 1987). However, other authors observed preserved suppressive effects after delays of several minutes (Li, 1993) or even hours (Fahy, 1993) (see below). For some neurons activity reductions of over 50% are observed and some “fall asleep” completely (Ringo, 1996). The suppressive effect is likely to go along with a depression of synaptic effectiveness.

3.2 Evidence for the automatic engagement of repetition suppression by stimulus repetition

Repetition suppression plays a crucial role in rapid visual object recognition. Thereby it is not dependent on attentional resources or awareness, but rather constitutes an automatic mechanism for the detection of stimulus repetition. The effect is mediated by intrinsic properties of cell populations in designated brain areas. Evidence for the automaticity of repetition suppression comes from the following studies.

Probably the most convincing finding was made by Miller et al. (1991) who examined the responses of neurons in the inferior temporal cortex to repeated presentations of visual stimuli in anesthetized macaque monkeys. Stimuli were three-dimensional objects like plastic toys as well as photographs of such objects. Animals' eyes were focussed on a target screen and stimuli were either presented by hand (in case of the three-dimensional objects) or projected onto the screen. Presentation duration was 1s per stimulus. For interstimulus intervals of 2-12s decreased activity in the measured neurons was observed with the repetition of the stimulus. This suppressive effect was similar or even stronger in the anesthetized compared to awake animals.

In a different study by Miller et al. (1994) neuronal activity in the inferior temporal cortex of awake monkeys was tested in two different kinds of delayed matching to sample tasks. In the standard version a sample stimulus ('A') was followed by a sequence of test stimuli. Only the sample stimulus was repeated once in the sequence (for example 'BCDEA'). The animal could get a reward upon correct detection of the matching stimulus. In a variation of the delayed matching task (the 'ABBA' task) one of the intervening test stimuli was also repeated once in addition to the repetition of the task-relevant sample stimulus. A reward was only given when the animal responded to the repetition of the relevant test stimulus (i.e. 'A'). For both trials the majority of cells showed suppressed responses to any stimulus repetition regardless of whether task-relevant or irrelevant. This was not the case for non-matching stimuli, where the neural responses remained strong. These results demonstrate that repetition suppression occurs automatically and independently of task relevance at the detection of stimulus repetition.

The above studies provide evidence for the automaticity of repetition suppression in the process of recency detection. In a healthy subject this passive

neuronal mechanism is active whenever a repeated stimulus is detected. It occurs under anesthesia, passive fixation and is independent of attentional allocation and task-relevancy.

3.3 Onset and time course of repetition suppression

As outlined above, the particular brain areas showing repetition suppression are mainly the (anterior) inferior temporal and the inferior frontal cortex. This is consistent with the evidence implicating the inferior temporal cortex as the neural substrate for object representations (Ungerleider, 1994). Further, inferior prefrontal regions are involved in working memory for objects (Ungerleider, 1998) and have therefore representations of the latter. These areas lie in the mid of the stimulus processing hierarchy, preceded by basic visual processing and followed by higher cognitive processing and response output. Therefore the suppressive effect should be observable in a preferred time interval.

A first clue to the temporal onset of repetition suppression comes from the study by Begleiter et al. (1993), outlined above in more detail. In that study the repetition of a visual stimulus was associated with a significantly smaller amplitude in temporal regions around 240ms after its onset.

Li et al. (1993) reported the occurrence of repetition suppression in anterior inferior temporal cortex as early as 170-180ms after the onset of the second presentation of a sample stimulus. Recordings from single cells of rhesus monkeys were done. Initially novel complex photographs (for example faces, bodies, natural objects) were presented and followed by two to five test stimuli. The last stimulus in such a sequence was always the matching one. After 3 to 35 trials (that means after 25s to 5min) a sample stimulus that had already been used earlier, was used again as a sample in another trial. The focus of the study was not primarily the within-trial, but the across-trial effect. About one third of visually responsive neurons in the inferior temporal lobe exhibited a significant response suppression when a formerly novel sample was used again as a sample in a later trial. Comparing the first and second sample presentation across two trials, the neuronal activity and its time course remained similar up to 170-180ms. From this point on the response to the second sample presentation became suppressed. Comparing the responses to the

sample and its matching stimulus within one trial, when subjects had to actively respond to the matching stimulus, the suppressive effect started even earlier.

In two studies by Penney et al. (2001 and 2003) the question of the exact temporal characteristics of repetition suppression was further explored. The first study comprised two EEG-ERP visual target detection experiments. The task in both experiments was to press a button whenever a target stimulus was presented and to withhold the response in case of non-targets. Each target was presented only once, whereas half of the non-targets were shown two times. Repeated stimuli followed immediately their first presentation. In experiment 1, targets were drawings of possible (for example eye-glasses) and impossible (for example a part of a piano attached to a section of a car) real world objects. Non-targets were line drawings of possible and impossible 3-D geometric objects. Experiment 2 used similar stimuli except that targets were the geometric objects and non-targets were real world objects. Summarizing the results, repetition of both types of possible non-targets elicited less negative waveforms than their first presentation in frontal areas in a time range from 250 to 400ms. Similar findings were made for both types of impossible non-targets except that the effect took place in a slightly shorter time window from 250 to 350ms. The observed decrease in neuronal activity indicates that stimulus processing requires less effort at repetition. It is consistent with a facilitated access to the visuo-spatial representation. The fact that the repetition effect was found for possible and impossible real world objects and geometric shapes, stresses the facilitated activation of visuo-spatial, rather than semantic or verbal representations.

The second study was a MEG study that employed the brain surface current density (BSCD) reconstruction technique to determine the amount of activation changes when a stimulus was repeated. In one part of the study subjects were shown line drawings of geometric objects. Half of these stimuli were repeated once. This repetition immediately followed the first presentation. No behavioral response was required in these trials. As expected, a reduced neuronal response was measured when subjects were confronted with the familiar objects. This activity reduction was found in the time interval from 250 to 350ms.

These studies give a broad idea of when to expect repetition suppression in cortical areas. For inferior temporal regions single-unit recordings registered significant activity decrements at the second compared to the first sample presentation starting at 170-180ms. This was only the case when no behavioral

response to the presentation was required. When an active matching to sample task had to be performed, differences in activity to the repeated matching stimulus occurred even earlier. When EEG or MEG are employed, repetition suppression in frontal areas will be observed with an onset around 200ms and an offset about 150-200ms later.

3.4 Perceptual priming is mediated by repetition suppression

The behavioral phenomenon of perceptual priming is most likely linked to the physiological finding of repetition suppression. Perceptual repetition priming is a type of implicit memory that operates on a nonconscious and pre-semantic level (Tulving, 1990). Behaviorally the perception and identification of an object is improved by its repetition. The distinctiveness from explicit memory is shown for example by its preservation in amnesia, despite large impairments on explicit memory tasks (Hamann, 1997). The general behavioral properties of perceptual priming and their consistency with the neural features of repetition suppression are outlined by Wiggs (1998). First, perceptual priming is long lasting. It has been observed even after a delay of 48 weeks between the initial presentation of a stimulus and its first repetition (Cave, 1997). This corresponds well with the observation that repetition suppression is still in place after 24 hours. This was the longest delay tested after which neural activation was still decreased upon repetition of the stimulus (Fahy, 1993). In that study recordings of the activity of single neurons in the temporal lobe of monkeys were done during a serial recognition memory task using complex pictures. For a subgroup of tested neurons, response decrements to familiar pictures were still measurable after 24 hours. The authors related the decreased responses to priming memory, i.e. the facilitation of performance by a prior related event. Second, priming is an incremental process, meaning that its behavioral benefit increases with multiple repetitions (Brown, 1996). Repetition suppression is also graded. Li (1993) found that the suppressive effect became gradually stronger with successive repetitions, until after six to eight repetitions responses reached a plateau that was approximately 40% of the peak response. A third characteristic of perceptual priming is its robustness to alterations of stimulus attributes like luminance, contrast, color, location, or size (Srinivas, 1996 a + b). It is only disrupted when physical attributes

that are essential to the physical form are altered. Similarly repetition suppression remains intact after changes of size or location of the repeated object (Lueschow, 1994). Further, the independence of perceptual priming as well as repetition suppression from attention or even consciousness has been confirmed. Priming occurs even to irrelevant or unattended stimuli (Szymanski, 1996) and also under anesthesia (Kihlstrom, 1990). Both observations have also been made for repetition suppression (Miller, 1994; Miller, 1991). Finally, both perceptual priming and repetition suppression have been demonstrated to span interfering or intervening stimuli (Bar, 1998; Li, 1993).

These similarities make the neural mechanism of repetition suppression a perfect candidate for the behavioral phenomenon of perceptual repetition priming. Many imaging studies investigating perceptual priming have found decreased neuronal activity upon repetition of the target stimuli (see above). Perceptual priming is distinguished by many of the above characteristics from explicit memory. Priming is also distinguished from explicit memory by its ontogenetically earlier emergence. From the age of 3 years it remains relatively stable throughout life (see for example Rybash, 1996, and Mitchell, 1993). Priming therefore represents a more basic and primitive type of memory. The underlying repetition suppression is an intrinsic property of cortical neurons. Priming provides one type of perceptual learning that allows a rapid and efficient identification of previously seen stimuli.

3.5 Affective modulation of repetition suppression

Only two studies exist to date that give clues to the question of whether repetition suppression is modulated by emotion. Deduced from the evolutionary perspective that it is particularly important for an organism to reliably identify the presence of a threatening stimulus, repetition suppression may be stronger for highly relevant threat-stimuli. As outlined above, with repetition of a stimulus the pool of activated neurons in a network is supposed to be reduced so that only neurons remain active that encode essential stimulus features. This leads to a faster and more accurate stimulus processing. A stronger repetition suppression might be the basis for an even more efficient processing of dangerous or threatening stimuli.

Ishai (2004) investigated this issue in a fMRI study employing a face working memory task. A group of healthy subjects watched a target face for 4s that should be memorized. Whenever the subject detected the reoccurrence of the target within a subsequent sequence of face stimuli, a button should be pressed. The sequence consisted of three repetitions of the target and seven novel distractors. All stimuli in the sequence were intermixed and presented for 2s each. Target and distractor stimuli were gray-scale photographs of either neutral or fearful facial expressions. Repetition suppression was significantly stronger for fearful than for neutral target faces. This effect was also correlated with the behavioral reaction times, which were faster for fearful targets. The affective modulation of repetition suppression might be achieved by feedback projections from the amygdala. The representation of emotional stimuli is sharpened more compared to neutral items. This reflects the importance of responding efficiently to biologically relevant stimuli.

A fMRI study by Bentley (2003) found additional support for the emotional modulation of repetition suppression, regardless of whether stimuli were attended or unattended. The authors investigated the influence of attention and emotion on the modulation of repetition suppression. The employed matching task started with the presentation of a cue stimulus that indicated via highlighted frames whether subjects had to attend to horizontal or vertical locations in a cross-format spatial array for performance of the subsequent matching task. The upcoming stimuli in the non-highlighted frames were to be ignored. This frame cue was presented for 2s and was followed by a four-picture display. This display consisted of a pair of faces (either neutral or fearful expressions) and a pair of houses. The face pair was either in the attended (task-relevant) or unattended (task-irrelevant) location (frame). It was repeated once after a lag of 2 to 5 intervening trials. Houses were never repeated. Picture array presentation always lasted 250ms. Subjects had to indicate by button-press whether the two stimuli at the task-relevant locations were the same or different. The measurements revealed that attention had no influence on the observed repetition decreases in bilateral inferior temporo-occipital cortex and left inferior prefrontal gyrus. Decreased activation was found in response to the repetition of both attended and unattended stimuli, suggesting that repetition suppression is an intrinsic property of cell populations in the respective areas. Furthermore, repetition suppression was greater for fearful than for neutral faces in extrastriate visual areas.

The two outlined studies give evidence for an emotional modulation of repetition suppression. It seems more important for an organism to respond rapidly and efficiently to the reoccurrence of a threatening than of a neutral stimulus. This is achieved by an even stronger repetition suppression that represents the sharpening of the stimulus representation in frontal and temporal brain areas. It is reasonable that this effect is independent of selective attention.

3.6 Repetition suppression in PTSD

It was first hypothesized by Davidson (2004) that anxious individuals may show minimal repetition suppression in response to fearful or threatening stimuli. However, this question was never systematically addressed in investigations to date. There is only one study that focussed on the repetition effects in the lateral occipital cortex when veterans with and without PTSD viewed combat- and non-combat-related visual stimuli. Hendler (2001) employed a covert “one-back-matching” task in a fMRI study with combat veterans, half of which had a diagnosis of PTSD, the other half not. Two conditions existed, one (‘Rep’) in which the same picture was repeated several times and in the other (‘Diff’) different pictures were shown and each slide appeared only once. A block-design of presentation was used. In the Rep condition some of the pictures were reduced in contrast but stayed otherwise the same. Pictures were either combat-related or of civilian content. Subjects always had to decide whether the present picture matched the previous one. The fMRI results indicated a significant signal reduction in the Rep as opposed to the Diff condition for both groups. Further, the PTSD group showed a weaker suppressive effect than the non-PTSD group only for the repeated combat slides. This study demonstrates a disturbance of the processing of trauma-related visual stimuli at the perceptual level. As outlined above, repetition suppression has been observed in occipital brain areas, too (Ishai, 2004), but the majority of studies have located this effect in temporal and prefrontal areas. The study by Hendler has shown a reduced repetition suppression in the occipital cortex of PTSD subjects when trauma-related pictures have been repeated. No studies exist to date that have tried to expand these findings to temporal and prefrontal cortex.

3.7 Summary and hypotheses for the present study

Talking in terms of Li (1993), the mechanism of repetition suppression might be regarded as an adaptive mnemonic filter. A novel stimulus will activate this filter which in turn will drive attention and orientation towards this stimulus. As a result of repeated exposure, synaptic weights in the neuronal network initially representing the novel stimulus will be changed. With repeated exposure, only neurons essential for object recognition will remain active, thereby reducing the overall activity in the network. This means that the 'elimination' or inhibition of certain neurons from the network leads to a sharpened stimulus representation. Further repetitions of the stimulus promote the shrinkage and shaping of the neuronal stimulus representation, thereby leading to a more rapid and better stimulus recognition. With repeated exposure to the stimulus, less attention and resources are necessary for its processing. This is usually associated with a behavioral habituation. Moreover, the system's freed processing resources can be employed for other competing stimuli. The associated brain areas keep an implicit memory (priming) of the now familiar stimulus. A schematic model of the interaction between memory and attentional systems is given in Figure 5.

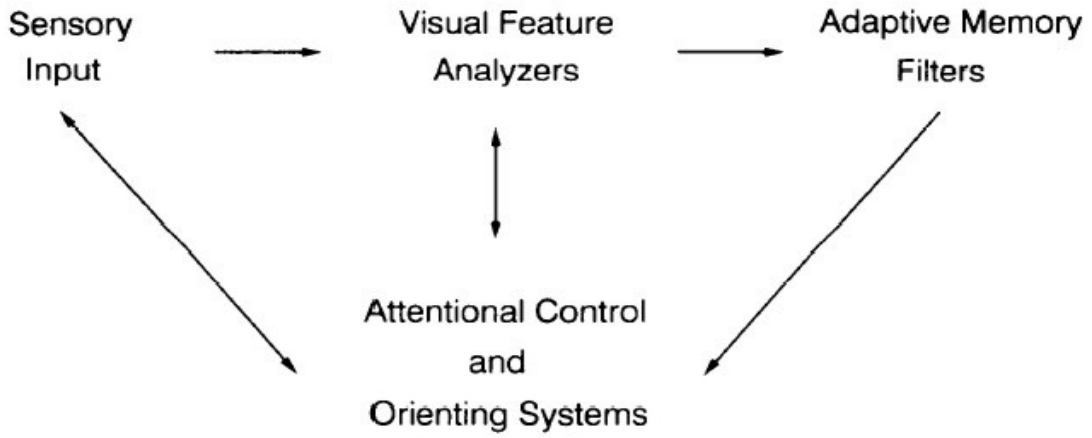


Figure 5: A novel stimulus will activate an adaptive mnemonic filter which in turn will drive attention and orientation towards this stimulus. As a result of familiarity, synaptic weights in the neuronal network initially representing the novel stimulus will be changed. This leads to a sharpened stimulus representation and a reduced overall cortical activity, due to the dropping out of "irrelevant" neurons. Together with a behavioral habituation across repeated exposure to the stimulus, processing resources will be freed for other stimuli (Figure taken from Li, 1993).

The decreased activity in a neuronal population after repeated exposure to a stimulus signals that the current stimulus is not novel anymore and therefore deserves less attentional and general processing resources.

A reduction or lack of repetition suppression would mean that subjectively a given stimulus is continuously regarded as 'novel' and requires further attentional focus. Likewise a behavioral habituation to this stimulus does not take place. Processing resources are occupied primarily with the processing of the stimulus at hand. This might be the case in PTSD.

Generally each complex visual scene consists of multiple cues (or objects, elements). According to the competition bias hypothesis, these multiple cues compete with each other for attentional selection (Desimone, 1995). Each cue activates its respective neural representation in the cortex. An individual may regard certain stimuli from the scene as more or less relevant, depending partly on his/her prior experience with these stimuli. For a PTSD patient threatening cues will be more relevant than for someone who has no experience with such a threatening stimulus. A healthy subject will show a behavioral habituation and repetition suppression to a threat-stimulus with increasing experience with the stimulus. The neuronal representation of the stimulus will be sharpened. Due to the additionally freed processing resources, he/she will further be able to rapidly integrate other competing stimuli from the scene. For example a scene is comprised of a snake and different contextual stimuli. A snake in the wild is a potentially dangerous cue, whereas a snake in a cage is not. The cage is a contextual stimulus that makes a harmful scene a harmless one. A healthy subject will rapidly integrate the cage stimulus with repeated exposure. On the other hand, some evidence exists that PTSD subjects have disturbances in the processing of 'contextual' information when a threatening cue is present. Therefore, contextual stimuli that are present at the same time as the threatening stimulus and that may signal the harmlessness of the complete scene are neglected by a PTSD patient. A reduced or lack of repetition suppression could be the neuronal correlate.

In the following, examples of studies showing selective processing in PTSD are given. Bryant et al. (1997) measured attentional bias for threat-related stimuli in PTSD subjects using the dot-probe paradigm. A threat and a neutral word (distractors) are simultaneously presented in two distinct areas of the visual field. Then a neutral target word ('left' or 'right') is shown either in close proximity to the

neutral or the threat word. The subjects' task is to respond to the detection of the target word. The proximity of the target word to the other stimulus word is the essential factor in this design. In addition to a threat word, a positive word was alternatively used to test for general effects of emotionality. It was shown that PTSD patients named targets more rapidly when they were adjacent to threat words compared to a larger distance. This was not the case when a positive word was used. Control subjects did not show this effect. It was concluded that PTSD subjects, due to their hypervigilance to threatening information, show a visual attention bias to threat stimuli. Threat words attract the subjects' attention and therefore stimuli in close proximity are recognized more rapidly than more distant stimuli. This finding also implies that stimuli farther away are not processed as effectively as stimuli close-by.

Similar results were found by Chemtob et al. (1999). In their study the disturbance of shifting attention from a trauma-related stimulus to a more neutral one was investigated. A distractor slide in form of either trauma-related pictures or neutral content was presented. About five seconds later a five digits string was projected in one quadrant of the distractor slide so that both slides were visible at the same time. The task was to detect the presence or absence of the target number '4' within the digits string. The dependent variable was the response latency. Altogether four groups were tested. A combat-related PTSD group, a non-PTSD combat, and a non-combat control group, as well as a psychiatric control group of patients with other diagnoses like simple phobia, panic disorder, generalized anxiety disorder, or major depression. Compared to all control groups, the PTSD group had significantly longer response latencies exclusively when the trauma-related distractors were present, but not when neutral distractors were used. The trauma-related stimuli captured the attentional resources of PTSD patients, resulting in an interference with the performance in the concurrent digit detection task. The authors hypothesized that the deficit represents the inability to disengage from trauma-related stimuli in favour of other neutral environmental stimuli.

These studies correspond with PTSD subjects' reports that they often have difficulty in attending to every-day tasks when stimuli are present that are potential reminders of the traumatic event. These reports underline the disturbances in attention shifting from threatening to other 'contextual' cues.

For the present study it is hypothesized that PTSD patients show a reduction or lack of repetition suppression when threatening stimuli are repeatedly seen. The effect should be measurable in inferior temporal and inferior prefrontal brain areas. In contrast to PTSD, healthy control subjects are expected to show a marked suppressive effect upon the repetition of fearful pictorial stimuli. According to earlier studies on repetition suppression (Begleiter, 1993; Li, 1993; Penney, 2003) its onset is expected around 200ms after the onset of the repeated stimulus and its offset should be observed up to 200ms later. Since repetition suppression is an incremental process (Li, 1993), the suppressive effect in healthy controls should be more pronounced in response to the second stimulus repetition. In PTSD subjects attentional and general processing resources are guided towards the threatening stimulus and will stay there across repetitions. The particular fearful stimulus will remain 'novel' in terms of a lack of neuronal response adaptation. It is hypothesized that specific trauma-induced alterations of neurons involved in implicit visual memory result in biased attentional selection processes. The threat-related stimulus will capture and maintain attention across repeated exposures.

4 Psychopathology determines selective activation of associative sensory-perceptual episodic memories in a picture recognition task

Based on the model by Conway (2001, see below) episodic memory contains highly detailed sensory-perceptual memories of experiences. In healthy subjects episodic memory is integrated into and 'framed by' autobiographical memory. In analogy to Metcalfe and Jacobs (1996), the autobiographical context memory that has the function of grounding the self can also be termed "cold" memory, whereas the highly sensory-perceptual episodic memory can be termed "hot" memory. Autobiographical memory is a form of memory characterized by individual personal episodes that are definable with respect to time and place. Recollections of these memories can have 'near-experience' quality, with reactivation of vivid sensory-perceptual details, thoughts, and emotions, if episodic memory is accessed. The anatomical substrate of autobiographical memory is the temporal lobe. Evidence for this attribution comes from several imaging, ERP, and lesion studies. Medial structures like the hippocampus and amygdala are activated whenever emotional episodes of one's own life are remembered. In addition, ventral areas that comprise the ventral visual processing stream are activated when a person recollects internal pictures of prior life events. This neocortical activation is strongly modulated by the amygdala, probably via cholinergic projection neurons. Highly emotional events are retrieved with concomitant higher neocortical arousal for example in visual processing areas. In a range of ERP studies, episodic memory is simulated by employing recognition memory paradigms. Visual stimuli like faces, non-verbalizable shapes, or pictures of common objects are repeatedly shown and the changes in ERP responses upon repetition are indicative of memory processes. The most prominent ERP repetition effect is a positive-going shift of the N400/P600 complex. This effect is diminished or absent in patients with damage or removal of parts of the temporal lobe. Patients suffering from PTSD often have intrusive thoughts and accompanying vivid visual recollections of their traumatic life events. The recollection of these scenes is highly sensual and emotional and can have the quality of flashbacks because of the separation of the "hot" and the "cold" system. These patients are further thought to have a hyperresponsive amygdala. It is hypothesized in the present study that emotional pictures act as triggers for the activation of episodic neuronal networks within the temporal lobe. This should be a differential effect that is strongest for

aversive slides as compared to positive or neutral. It is expected that the hyperresponsive amygdala in PTSD patients enhances memory systems in the temporal lobe upon exposure to trauma-related pictures. Furthermore, this enhancement should be associated with a better recognition performance for these kinds of stimuli. In the following sections supporting evidence for the outlined theoretical model is presented.

4.1 Role of the temporal lobe in episodic memory

4.1.1 Conway's autobiographical memory model

Conway provides a theoretical framework for the organization of autobiographical memory (Conway, 1993; 2000). He proposes three levels of abstraction of autobiographical memory. The highest-ranking level comprises 'lifetime periods' with their period-spanning particularly dominant feelings and evaluations as well as information about locations, activities, and persons (for example 'at high school'). The next lower level consists of memories of 'general events'. This refers to extended events or events that occurred repeatedly in one's biography (like 'going hunting'). The lowest level refers to single events of usually short duration (minutes – hours) and the memory for these events contains highly specific, sensory-perceptual internal details (Conway, 2001). This type of memory is termed 'episodic memory'. Recollections of these memories can have 'near-experience' quality. Conway further concludes that these highly sensory memories are represented in the brain regions that were also involved in the processing that took place during the actual event. For visual experiences this means that the temporal cortex that contains the ventral visual processing stream is also involved in their recollection. The ventral stream is responsible for object recognition and is traditionally associated with the storage of visual long-term memory.

Bayley et al. (2005) studied episodic memory in patients with damage limited to the medial temporal lobe and in a group with significant additional damage to the neocortex. The more severe memory impairments of this latter group stress that the ability to recollect remote autobiographical events strongly involves the temporal and other distributed neocortical areas.

For a contextualized and structured recollection of these memories, not only temporal cortex is crucial, but also the hippocampus. According to the 'Multiple Trace Theory' of memory (MTT) (Nadel et al. 2000), the hippocampus involvement remains always necessary for the storage and also the retrieval of episodic, but not of semantic memories. Thereby the model distinguishes between the neural underpinnings of semantic and episodic memory. For episodic memory it is supposed that various parts of a particular episode (sights, sounds, smells,…) have representations in distributed cortical areas. These have to be 'bound' for later retrieval. The MTT declares that the hippocampus is always needed for this integrative process and for a holistic memory retrieval. The hippocampus is assumed to be the crucial structure that binds content and context information like time, place, emotional content, and perceptual features that are required for the experience of recollection. Hippocampal memory traces are regarded as the basis for the reactivation of cortical traces. In case of flashbacks seen in PTSD, the disturbing 'here-and-now' quality of this phenomenon is due to a lack of contextual information that relates the memory content to the past history (see also Elbert, 2002). A hippocampal dysfunction at the time of encoding is supposed to be responsible for the detachedness of the "hot" from the context memory. Furthermore, in victims of multiple traumatic experiences the high number of events provides more and more conflicting information. Typically a person can only retrieve one context in which the fear network was previously activated. With increasing number of traumatic events the associative fear network expands and interconnections become stronger. In parallel the likelihood of the coactivation of the declarative memory system decreases, further contributing to the lack of contextual information (see also Elbert et al., 2006). Reduced hippocampal activity has been associated with more severe PTSD symptoms (Astur, 2006).

Evidence for the necessity of hippocampal involvement in the retrieval of context information comes for example from a fMRI study by Ryan et al. (2001). Subjects had to retrieve remote autobiographical memories that occurred either within the last 4 years or more than 20 years ago. During recollection bilateral activation of the hippocampus was measured in both conditions. The authors further hypothesized that reactivation of remote events creates new memory traces within the hippocampus, and that possibly old ones are strengthened.

4.1.2 The role of the temporal lobe in autobiographical memory – evidence from brain damaged patients

Steinvorth et al. (2005) conducted an extensive declarative memory study with two amnesic patients with bilateral medial temporal lobe lesions and a healthy control group. Episodic memory was investigated employing the Autobiographical Interview developed by Levine et al. (2002) that is designed to see how well subjects are able to re-experience personal happenings from the past. Participants were required to recall one specific personal life event from each of five life periods: childhood, teenage years, early adulthood (for example wedding), middle age, and the year prior to the study. The most important characteristic of this test is that in addition to a spontaneous recall, subjects are asked in a standardized and structured manner to recall highly specific information such as sounds, sights, smells, or emotions. Such internal details reflect the episodic re-experiencing. Subjects were also asked to rate the vividness of each memory, the emotional change elicited by the event, and its personal importance. The test also includes the recollection of external details that are rather semantic than episodic (factual information). Evidence was gathered that remote semantic memory was virtually preserved in the two patients. Their results for semantic memory were comparable to those of the controls. Contrary, a severe impairment for remote episodic memory was uncovered for the patients. The controls provided significantly more internal details for all recalled life events. They also rated most of the recollections as more vivid compared to the patients. These results stress the role of the medial temporal lobe for autobiographical memories. The type of episodic memory required in the Autobiographical Interview can be regarded as experience-near, highly specific, sensory-perceptual details of personal life events. Exactly this type of memory could not be recalled by the patients.

A recent MRI study by Gilboa et al. (2005) further stresses the important role of the medial and lateral temporal lobe in the retrieval of episodic memory. Patients with mild Alzheimer's disease with varying degrees of retrograde memory loss were studied. Autobiographical memory for episodes from childhood, adulthood, and recent past was assessed. Subjects had to provide the temporal and spatial context of certain events and their reports were rated for descriptive richness and specificity. In addition, the number of reported details was scored. Impairments for all these episodes were associated with combined atrophy in bilateral medial temporal lobe

and anterior lateral temporal neocortex. The amount of tissue loss from anterior temporal cortex and medial temporal structures was strongly related to the severity of autobiographical memory impairments. The multivariate analysis technique of Partial Least Squares (McIntosh, 1996) was used to identify assemblies of brain regions that together covary in relation to behavioral measures. Results yielded a group of regions consisting of the bilateral medial temporal lobes and anterior temporal cortices, as well as the right lateral posterior cortex that was associated with the performance on autobiographical memory tasks. These finding stresses the involvement of both medial and lateral structures in the retrieval of episodic memory.

Spiers et al. (2001) employed a 'real-world'-like experimental design in order to investigate recent autobiographical memory. In their study, subjects made experiences in a virtual 3-dimensional town. Later, context-dependent memory about virtual encounters with other characters in the town and topographical information were assessed. Subjects were patients with either left (LTL), or right (RTL) temporal lobectomy, and a healthy control group. The results can be summarized as follows: compared to the healthy controls, both patient groups showed significant deficits in all memory tests. The RTL group was most impaired in all topographical memory tests and in object recognition, whereas the LTL group showed the most severe deficits in the memory tasks in which various aspects of the encounters were asked. These findings demonstrate that bilateral medial temporal lobe structures are involved in topographical and autobiographical memory processes, but that some degree of lateralization exists. The right hemisphere seems to be more involved in topographical tasks and object recognition, whereas the left hemisphere is more concerned with context-dependent autobiographical memory.

Thus, the above lesion and lobectomy studies show that context-rich episodic memory depends on neuronal ensembles in bilateral medial temporal lobe – neocortical networks. Cortical structures are thereby supposed to be involved in the retrieval of sensory-perceptual memories.

4.1.3 Autobiographical memory in the temporal lobe – findings from PET and fMRI studies

The role of the temporal lobe for episodic memory was confirmed in a number of imaging studies. Fink et al. (1996) for example investigated the neural networks involved in the retrieval of personal episodic memory. During a PET scan, subjects listened to sentences containing affect-laden autobiographical (PERSONAL) information. Auditory information was presented that contained information from the subjects' childhood, adolescence, and early adulthood (for example: "When you were 15 you took part in a swimming marathon…"). Subjects were required to imagine in detail what had happened. Information about significant events was gathered some weeks prior to the experiment. Further, a baseline REST condition was implemented without any auditory material. Comparing the two conditions, increases in neural activity were observed in the temporal lobes including the temporal poles, the medial and superior temporal gyri, and hippocampal, parahippocampal, and amygdaloid regions. Further, dorsal frontal and right posterior cingulate areas were active. Thus, these findings demonstrate the essential role of the temporal lobe in the retrieval of personal episodic memory.

Similarly, Piefke et al. (2005) investigated the functional neuroanatomy subserving episodic memory in a fMRI study. Subjects were required to remember as vividly and emotionally as possible personal biographical events with positive and negative valence. Compared to baseline, neural activity was increased in medial and lateral temporal areas that included parahippocampal and hippocampal regions.

These two studies are examples of investigations demonstrating a heightened neural activity in the temporal lobe when subjects retrieve autobiographical events. A complete overview of studies further supporting this observation can be found in Moscovitch et al. (2005).

4.2 The temporal lobe as a generator of the N400/P600 repetition effect

A general finding of ERP studies employing recognition memory tasks is that correctly detected 'old' items produce a greater positivity in the ERP signal compared to 'new' items (e.g. Friedman, 1990). As will be further outlined, this effect seems to

be the result of the modulation of two distinct but functionally correlated components: a negative waveform around 400ms (N400) and a subsequent positive component peaking around 600ms (P600). The most likely local generator of this ERP 'old/new' effect is the temporal lobe. Evidence for this hypothesis comes mainly from studies investigating patients with temporal lobectomy and studies applying intracranial depth recordings.

Rugg et al. (1991) investigated the ERPs of temporal lobectomy patients, whose surgery involved the removal of the anterior part of either the right or left temporal lobe, including lateral and medial structures, in a continuous verbal recognition task. Subjects had to indicate whether a word was shown for the first time or was repeated. Results were compared with a group of healthy controls and a group of temporal lobe epilepsy patients. Controls showed the expected ERP 'old/new' effect in the time range from 300-600ms with a positive-going shift upon stimulus repetition, whereas lobectomy patients' 'old/new' differences were abnormally small and did not differ significantly from zero. The epileptic patients showed similar mean 'old/new' effects like the healthy controls, although the effect was smaller over the hemisphere ipsilateral to the epileptic seizures as compared to the contralateral side. It was concluded that unilateral temporal lobectomy is associated with attenuated 'old/new' ERP effects. In addition it was shown that less severe temporal lobe abnormalities than lobectomy can also impair this effect, as indicated by the epileptic patients.

A recognition memory experiment by Puce et al. (1991) demonstrated a similar morphology and latency of the memory-related ERPs when visuo-spatial stimuli were used instead of verbal material. A sequence of abstract, non-verbalizable shapes was presented. At a random point during the trial each item was repeated once. The minimum time between repetitions was 45s. Subjects had to categorize stimuli as either novel or repeated via button press. Subjects were patients undergoing epileptic surgery. Intracranial ERPs were recorded from the bilateral temporal lobes. Two ERP components were found. The first one was a negative component peaking at around 400-600ms after stimulus onset and was reffered to as N400. The second was a positive component reaching its maximum amplitude between 600-1000ms poststimulus and was referred to as P600. When a stimulus was repeated, both the N400 and the P600 were significantly more positive going. The N400 was bilaterally reduced in amplitude when a a slide was repeated,

the P600 amplitude was enhanced. Although this amplitude rise of the P600 was larger in the right hemisphere, significant effects were found bilaterally. To ensure that the observed ERPs were specific to recognition memory and not for example to the behavioral response or to a simple visual response, control tasks were included. In a passive control task novel stimuli were seen without the need of a behavioral response. No ERP response was elicited in this task. A further visual discrimination task also failed to generate a N400 or P600. Therefore the observed ERPs are specifically generated by recognition memory tasks. The authors pick up the hypothesis that the N400/P600 ERP complex represents a unitary functional component, but that both peaks subserve different aspects of information processing. The N400 is thought to be related to the processing of novel information, whereas the P600 to the recognition of familiar stimuli. This means that the N400 becomes smaller when a stimulus is not novel anymore and at the same time the P600 is augmented as the stimulus becomes familiar. This study shows that visuo-spatial recognition memory tasks produce the same ERPs like their verbal counterparts.

Guillem et al. (1995) investigated the anatomical locus of the generators of the N400/P600 complex by use of intracranial recordings in a range of brain areas while subjects performed a continuous recognition memory task. Furthermore, the modulation by repetition was addressed. 240 pictures of line drawings of common objects were used. Some of these pictures were repeated after 6 to 19 intervening items. A button press was required when a repeated slide was identified. Electrodes recorded from neurons in the temporal, frontal, parietal, and occipital lobes of patients undergoing epileptic surgery. Within the temporal lobe, medial and lateral neocortical areas were investigated. In both these regions a large amplitude negativity with a peak around 400ms and a subsequent positive component peaking at 650ms were found. When pictures were repeated, both components showed a significant positive-going shift. In prefrontal areas the amplitude of the negative component around 400ms was relatively low, suggesting no major contribution to the N400. In addition, a prefrontal P600 was found that occurred 100ms earlier and that had a slightly different morphology compared to the temporal P600, indicating that the temporal and prefrontal P600 do not reflect the same neural and cognitive processes. The results from the parietal lobes suggested some contribution to the scalp-recorded N400, but no major contribution to the P600. The results for the occipital lobe were negligible for the present context. It can be concluded from this

study that the ERP repetition effect is a memory-related modulation of the N400/P600 complex that is generated predominantly in the temporal lobe.

Altogether the ERP responses to repeated stimuli (words or pictures) in the medial temporal lobe are more positive going compared to novel stimuli in a late time interval from 400 to 600ms. The two ERP components N400 and P600 might reflect different cognitive processes, but they form a functional unity in memory processing.

4.3 Long-delay 'old/new' ERP effects as correlates of episodic memory retrieval

It has been outlined above that repeated exposure to a stimulus results in a modulation of both the N400 and the P600 ERP components. When a stimulus is repeated, a positive-going shift is observed that attenuates the peak of the N400 and augments the P600 amplitude. Behaviorally this repetition effect is manifest in shorter stimulus response latencies at the time of repetition. It has been hypothesized that short-delay repetition effects are associated with semantic activation and that long-delay repetition effects reflect activation of a long-lasting episodic mechanism (Guillem, 1999). In a study by Bentin (1988), behavioral effects of repetition of unfamiliar faces were investigated when subjects performed two different tasks. Facilitation of reaction time was the dependent variable. Faces were repeated with either 0, 4, or 15 intervening items between the first and second presentation. When a structural classification (face/non-face) was required, the repetition effect was rather short-lived and occurred only in the '0-lag' condition. Only upon immediate face repetition, classification time declined. For this kind of task no conscious recall of the priming stimulus is necessary. The observed short-delay repetition effect may be due to a short-lasting change in the accessibility of the stimulus representation, which might be semantic. On the other hand, when a recognition judgement was required, the repetition effect also occurred after long delays. For a recognition judgement, explicit awareness of the occurrence and identity of the prime is necessary. It is suggested that this long-delay repetition effect depends on the availability of a preexisting episodic memory trace. Forster and Davis (1984) propose that this stable long-term repetition effect reflects the reaccessing of the episodic memory trace that was established in relation to the context-specific presentation of

the stimulus. This trace is enhanced by subsequent re-presentation of the same stimulus.

Guillem et al. (1999) investigated the anatomical structures underlying the two distinctive systems of semantic and episodic memory. They hypothesized that brain areas associated with semantic processing would show short-delay repetition effects, whereas long-delay repetition effects should occur in areas related to episodic processing. Intracranial ERPs were recorded from a group of epileptic patients who performed a picture recognition memory task. Subjects had to respond to the repetition of a stimulus by a button press. Two sequences of line drawings of objects were presented in which half of the slides were repeated. In one sequence, 6 intervening items lay between the first presentation of a stimulus and its repetition (short-delay condition), in the other 19 items (long-delay condition). Each stimulus was presented for 1s and the interstimulus interval varied from 3 to 5s. Recordings were derived from three main functional brain areas: anterior temporal lobe (including amygdala, hippocampus, and anterior temporal cortex), posterior cortices (including parietal cortex and posterior temporal lobe), and frontal lobe (anterior cingulate, lateral frontal cortex, and orbital cortex). The following areas showed a significant repetition effect in form of a positive-shift of the N400/P600 ERP complex at both time lags: anterior temporal lobe and orbitofrontal cortex. This was taken as evidence that these structures are involved in episodic processing. Classical neuropsychological studies support the view that the anterior temporal lobe is concerned with episodic memory. Lesions to this structure produce severe memory disorders (e.g. Smith, 1989). The role of the orbitofrontal cortex in episodic processing seems to be a more directive, controlling one that influences the retrieval of episodic memory. The classical role of this structure is to deal with stimulus interference and therefore it might not be directly involved in episodic memory. All other investigated brain areas did not show long-delay repetition effects but only short-delay effects indicating their contribution to semantic processing. Posterior cortical areas for example seem to be involved in semantic processing as indicated by studies with patients with herpes simplex encephalitis (Warrington, 1984) or progressive cerebral degeneration (McCarthy, 1988). All these patients show posterior brain damage correlated with impaired semantic memory. The lateral frontal cortex also showed only short-delay repetition effects. This is in line with patient studies demonstrating that these areas are not essential for episodic memory.

Patients with damage to these regions do not develop a full-blown amnesic syndrome (Mayes, 1983). The conclusion from these findings is that the anatomic substrate of semantic processing is a widely distributed network that includes the posterior-parietal regions, as well as the dorsolateral prefrontal cortex and anterior cingulate. These regions showed only short-lived intracranial repetition effects. Contrary, the medial temporal lobe together with the anterior temporal cortex and orbitofrontal regions were characterized by long-delay repetition effects. It was suggested that these areas represent the neuronal basis of episodic memory.

4.4 Modulation of episodic memory by emotion

Emotional salience plays a crucial role for the initial sensory processing of a stimulus. The evaluation of a stimulus as being significant in either an appetitive or aversive way has an impact on the processing in the sensory cortex. The amygdala is the most likely candidate for modulating cortical arousal in these areas. The processing of an emotional stimulus is associated with an enhanced cortical activity. But this augmentation of activity in sensory cortical areas is not limited to the time when a stimulus is engaged for the first time. Emotional modulation takes also place when a stimulus is retrieved from memory. Episodic memory is characterized by detailed emotional and sensory-perceptual information. When emotional events are retrieved, activity in sensory cortex areas (for example in the temporal lobe) is modulated. Evidence for these mechanisms is outlined below.

4.4.1 Modulatory influences of the amygdala on visual cortical activation

The activation of visual cortical areas can be influenced by amygdala modulation. Thereby emotionally salient visual stimuli produce greater activity in these areas than neutral ones (Lang, 1998). It is a long established fact that the amygdala has extensive connections with a range of higher sensory processing areas. This includes projections to all major divisions of the temporal neocortex and especially to all levels of the ventral stream visual pathway (e.g. Amaral, 1984; 2003). Figure 6

shows a schematic picture of the anatomical connections between the amygdala and neocortical areas in the occipital and temporal lobe in the monkey.

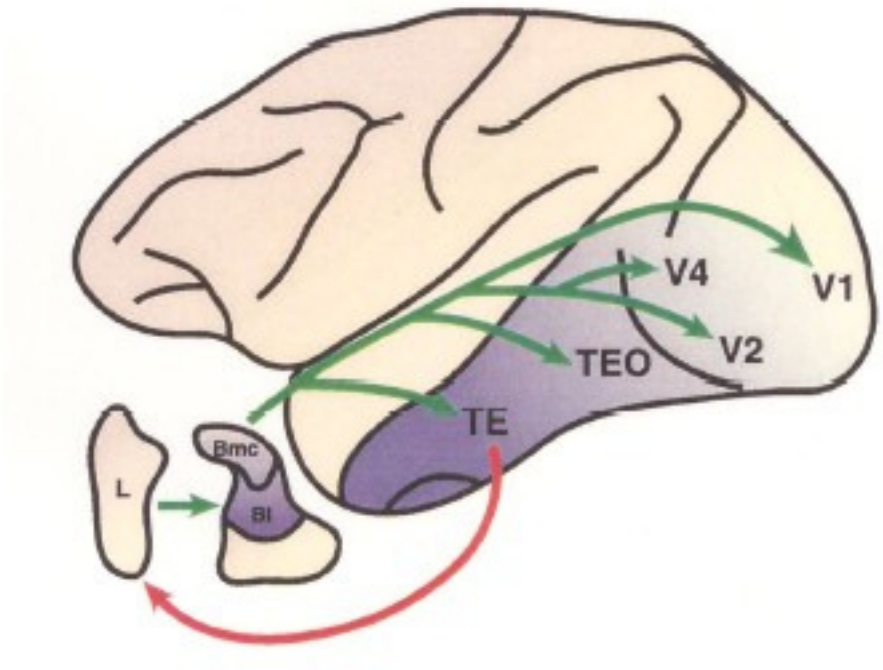


Figure 6: Projections from the amygdala reach primary and higher order visual processing areas in the occipital and temporal cortex. These connections are suggested to be the basis for modulatory amygdala influences on visual processing. Emotionally significant visual stimuli are associated with greater activity in visual processing areas compared to neutral (Figure is taken from Adolphs, 2004).

However, the functional role of these connections is a concern of recent investigations. Evidence is rising that emotion can influence visual sensory processing via these connections.

An animal study by Sugase et al. (1999) was one of the first studies to show enhanced visual cortex activity to threatening facial expressions versus neutral. The activity of single face-responsive neurons in the temporal cortex of macaque monkeys was measured when animals were exposed, among other stimuli, to colored pictures of monkey faces. The expressions of these faces were graded in four steps from neutral (close-mouthed) to very threatening (full open-mouthed). The two intermediate steps were pout-lips and mid open-mouthed. Comparing the two most threatening depictions with the other two expressions, neuronal discharge rates

revealed enhanced and more sustained activity in response to the threatening stimuli.

In further support of the idea that amygdala activity modulates cortical activity are the findings from an earlier study by Kapp et al. (1994). The authors applied electrical stimulation to the central nucleus of the amygdala in anesthetized and awake rabbits and measured a subsequent EEG desynchronization due to a suppression of slow delta waves. EEG desynchronization is a sign for heightened cortical arousal. This effect was markedly attenuated when cholinergic antagonists were administered. It was hypothesized that stimulation of the central nucleus has an excitatory influence on cholinergic cortical projection neurons of the nucleus basalis. Interconnections of the amygdaloid central nucleus and the nucleus basalis have been shown previously (Price, 1981). In a different study it was further shown that neurons in the central nucleus of the amygdala show increased firing rates when exposed to emotionally arousing stimuli (Pascoe, 1985) and that these kinds of stimuli elicit EEG desychronization (Kapp, 1991). Altogether these findings stress the modulatory role of the amygdala in influencing cortical arousal.

Summarizing these findings, the emotional salience or the behavioral relevance of a stimulus have an influence on the arousal level of sensory cortices. The amygdala evaluates a stimulus with regard to its emotional significance. Via cholinergic projection neurons to a range of neocortical areas, including the visual ventral processing steam in the temporal cortex, activity of these regions can be modulated. Thereby emotional stimuli are associated with an enhanced cortical activity. This modulatory effect is independent of attention.

4.4.2 The modulation of memory encoding and retrieval by emotion

A huge amount of evidence exists that memory for emotionally arousing events is better than for neutral events (e.g. Bradley, 1992). McGaugh's modulation hypothesis says that the beneficial effect of emotion on memory encoding and consolidation is due to amygdala modulation of the medial temporal lobe memory structures (McGaugh, 1996; McGaugh, 2000). Next to animal studies supporting this hypothesis (see Cahill, 1998 for a review), human evidence comes for example from a study by Dolcos et al. (2004). Using the subsequent memory paradigm, brain areas involved

in the encoding of emotional versus neutral pictures were identified with fMRI. High arousing emotional (both negative and positive were collapsed) pictures from the IAPS together with non-arousing neutral pictures were presented. Subjects were instructed to experience any feelings and thoughts that might be triggered by the slides and to rate each picture for pleasantness. The subjects did not know that 45min after the measurement a cued-recall test had to be done. Participants had to describe as detailed as possible the pictures they had seen. From the fMRI data, the activity difference between remembered minus forgotten emotional stimuli was calculated. The same was done for the neutral pictures, resulting in Dm (difference due to memory; Paller, 1987) for emotional and neutral stimuli. The behavioral results showed a recall advantage for emotional versus neutral pictures. Accordingly, the emotional Dm was significantly greater than the neutral Dm in the amygdala and the medial temporal lobe. Furthermore, a significantly greater positive correlation was found between the emotional Dm in the amygdala and the medial temporal lobe. This means that these two structures are coactivated more during the successful encoding of emotional compared to neutral pictures. These findings support the modulation hypothesis in demonstrating a strong interaction between amygdala and medial temporal lobe structures in the encoding of emotional material. The recall advantage for emotional episodic memory is achieved by the amygdala modulation of medial temporal lobe structures.

The memory enhancing role of the amygdala is not only due to its greater involvement at the time of encoding of emotional material, but also at the time of retrieval. This was demonstrated in another study by Dolcos et al. (2005). The same subjects tested in the earlier study (Dolcos, 2004) were tested again one year later for their retrieval performance of the same pictures they had seen one year before. The focus of this study was to identify the neural mechanisms that underlie the retrieval of remote episodic emotional memories. 180 old and 90 matched new pictures equally distributed across the valence categories ‘negative’, ’positive’, and ‘neutral’ were presented during an fMRI scan. Negative and positive pictures were later pooled to form the category ‘emotional’. Subjects had to indicate via button-press, whether they ‘remembered’ a picture, or whether it was just ’familiar’ to them, or if they thought it was a ‘new’ slide. When subjects ’remembered’ a picture, this meant that they actively recollected the item and the accompanying contextual information and other associated elements like time, location, and sensory details.

'Familiarity' meant that subjects had the feeling of having seen the picture but that they were not able to retrieve associated information. The active recognition ('remember') performance after one year was significantly better for emotional compared to neutral pictures. With regard to familiarity, no differences were found for the two categories. This effects was not due to better recall of the emotional pictures in the initial study, as indicated by a lack of a correlation between the performance in the recall and later recognition tasks. Activity in the amygdala and medial temporal lobe was greater for successfully retrieved emotional pictures than for neutral ones. This was an effect of active recollection and not of familiarity. Moreover, systematic coactivation between amygdala and medial temporal lobe was stronger for emotional items. Altogether the findings resemble the results from the prior study, in which activation was recorded during encoding. The same activation patterns were now found for long-term retrieval. It was further noted that it may be that the emotion-enhanced retrieval results from reinstating the affective context of the original episode that facilitates retrieval of contextual details. However, there is also the possibility that the recollection of these details reinstates the original emotional arousal.

The described studies demonstrate that the behaviorally observable memory advantage of emotional material has a neural underpinning in an enhanced activity of the amygdala and medial temporal lobe when emotional material is encoded and retrieved. Furthermore, a stronger coactivation between these two brain structures takes place during these processes.

4.5 Summary and hypotheses for the present study

Autobiographical memory refers to personal episodes or events in someone's own life. It is characterized by temporal and spatial context, as well as emotionality and sensory-perceptual impressions. The latter type of memory is referred to as episodic memory that is usually integrated into the more abstract autobiographical memory. Access to episodic memory can have near-experience like quality at retrieval (Conway, 2001).

The neural basis of autobiographical memory lies within structures of the medial temporal cortex and connected temporal cortices. Although memory

representations are stored in the cortex, the hippocampus is needed for a holistic memory retrieval. Thereby the hippocampus might have a 'binding' function. This model corresponds to the 'Multiple Trace Theory' of memory (Nadel, 2000). The involvement of the temporal lobe has been confirmed in imaging studies that showed activation of these areas when subjects remembered personal life events (Fink, 1996; Piefke, 2005). Further support comes from patients with damage to temporal brain areas. These patients show impairments in tasks of autobiographical memory recollection (Spiers, 2001; Gilboa, 2005) and a reduction of the ERP repetition effect (Rugg, 1991).

Recognition memory tasks are frequently used to investigate episodic memory processes. This paradigm has constantly been used in ERP studies of episodic memory. The most persistent effect is a positive-going shift of the N400/P600 ERP complex when a stimulus is repeated after a time lag filled with intervening items (e.g. Puce, 1991). The local generators of this effect have been shown to lie in the temporal lobe (Guillem, 1995).

Episodic memory encoding as well as retrieval are strongly modulated by emotional significance. Emotional events tend to be better remembered than neutral ones. As mentioned above, episodic memory has a highly emotional and sensory-perceptual component. When episodic events are remembered, cortical areas involved in perceptual processing are re-activated (Lang, 1998). This re-activation of sensory associative cortex areas that also serve as a long-term memory storage is responsible for the vividness of internal pictures of the event. The associated emotionality is 'provided' by amygdala activation that further enhances the arousal of the cortical areas (Sugase, 1999; Kapp, 1994). The temporal cortex comprises the ventral visual processing stream that is responsible for higher order visual processing. This region is particularly active when episodic memory is vividly re-experienced.

PTSD patients suffer from intrusive recollections of their traumatic events. These recollections are characterized by internal pictures of the event and high arousal levels. In the extreme case, flashbacks are elicited that are as vivid for the patient as if the event happens 'here and now'. Aversive pictures that resemble some aspects of the traumatic event can serve as triggers for these intrusive episodic recollections.

For the present study it is hypothesized that PTSD patients show an enhanced activity of neurons in the temporal cortex in a time range from approximately 400-600ms when repeatedly exposed to aversive pictures. The time interval is defined by ERP findings that showed repetition memory effects in this time range. The activity enhancing effect in temporal areas should occur particularly upon the second repetition of negative slides and not at the first repetition. This hypothesis is guided by the finding of Guillem (1999) who demonstrated that short-delay repetitions may rather represent the accessibility of a semantic stimulus representation and not episodic memory. In that study only long-delay repetition effects were associated with episodic memory retrieval. In the present study the first repetition occurs about 11s after initial picture presentation, the second repetition occurs approximately after 28min (see Methods section). It is supposed that the aversive pictures employed in the present study trigger trauma-related episodic memories in the PTSD group. The hyperresponsive amygdala in these patients might be responsible for the modulating effects on temporal cortex areas. Control groups with no prior history of traumatic events, and who do not have a hypersensitive amygdala, should not show this effect. It is further hypothesized that this effect is specific for negative pictures and that the enhanced activity in the ventral visual processing stream is correlated with a better behavioral recognition performance for aversive slides.

5 Collection of the hypotheses for the present study

a.) Evidence exists that PTSD subjects are characterized by a hypersensitive alarm system with the amygdala as the core structure for threat detection. The amygdala has strong connections to the OFC. Via these connections, information about the significance of a stimulus is transferred to the OFC for the guidance of goal-directed behavior. It is hypothesized that PTSD patients, as compared to non-PTSD control groups, show an early orbitofrontal activation exclusively in response to threatening stimuli. By use of MEG the exact temporal onset that is expected approximately around 100ms after stimulus onset is investigated.

b.) In healthy subjects exposure to a novel stimulus drives attention and orientation towards this stimulus. When the stimulus becomes familiar due to repeated exposure, a mnemonic filter is activated that leads to a shrinkage of the neuronal stimulus representation. Less attention and processing resources are required and are freed for competing stimuli. PTSD subjects are characterized by difficulties in shifting attention away from threatening stimuli. It is hypothesized that decreased repetition suppression in response to repeatedly seen threat-stimuli contributes to these difficulties. The hypothesized decrease is investigated in brain areas involved in object recognition. According to earlier findings, the effect should occur with an onset of approximately 200ms after stimulus onset.

c.) Episodic memories consist of highly specific sensory-perceptual, emotional details of prior life events. These sensory impressions are stored in distributed cortical networks. Visual memories are stored particularly in the temporal cortex that comprises the ventral visual processing stream. In PTSD subjects, exposure to threatening stimuli is expected to trigger the activation of these networks. It is hypothesized that repeated exposure to fear-relevant visual cues leads to spreading activation in the temporal cortex. This activation should be stronger in PTSD patients compared to controls. Furthermore, trigger stimuli are hypothesized to become rapidly integrated into the active fear network by association. This should lead to a facilitation of recognition memory for these stimuli, besides an otherwise impaired memory for positive and neutral cues.

6 Methods

6.1 Magnetoencephalography and source localization

Neuronal excitation results in an electrical potential distribution on the scalp and also produces biomagnetic fields of very low amplitude. The lines of magnetic flux surround the longitudinal axis of the electrical current that is evoked by a dipole. Magnetoencephalography (MEG) is a completely non-invasive technique for the measurement of these magnetic fields. The measurable MEG signal results from the synchronous summed mass activity of tens of thousands of cortical pyramidal cells. These cells constitute about 85% of cortical neurons. They are vertically oriented to the cortex surface. MEG measures the magnetic fields of dendritic currents of neurons that are oriented parallel to the skull surface. This means that mainly activity of cells within the brain's sulci is tracked. Nevertheless, some contribution to the magnetic field comes from neurons of intermediate orientation. They have both, radial and tangential current components of which only the tangential generates an extracranial magnetic field. Since the amplitude of brain magnetic fields is very low (below 1 pT, and around 100 fT for sensory evoked cortical magnetic fields), the development of superconducting quantum interference devices (SQUIDs) became necessary. These detectors have an unprecedented level of sensitivity when cooled down to about -270° C. Thus, the SQUIDs are enclosed in a so called 'Dewar' that is filled with liquid helium. The helium is necessary to keep the SQUIDs in the superconducting state. The Dewar with the insulated detectors and pick-up coils surrounds the scalp in a distance of about 10-15 mm, thereby covering the entire neurocranium. The Dewar is housed in a magnetically shielded room to prevent environmental magnetic fields from distorting the brain signal. With MEG, brain electrophysiology can be assessed in real-time due to the high temporal resolution in the milliseconds range. Of all non-invasive neuroimaging techniques, MEG provides the best balance of spatial and temporal resolution (for overviews see Elbert, 1998; Lewine, 1995). A picture of the MEG device can be seen in Figure 7. The MEG device used in the present study was a whole-head system with 148 channels.

Figure 7: MEG device. The SQUIDs with the pick-up coils are housed in a Dewar that is filled with liquid helium. The Dewar surrounds the scalp in a distance of about 10-15 mm. Experiments can be done in a supine or sitting position.

MEG has several advantages over electroencephalography (EEG). First, MEG is free of contact with the subject, which makes it particularly suitable for clinical patient studies. Second, in contrast to EEG, which measures the electric potential distribution brought to the scalp by the extracellular volume current, MEG registers the magnetic fields that result from intracellular currents. This has the advantage that distortions due to different conductivities of the different extracellular tissues like scalp, skull, cerebro-spinal fluid etc., can be excluded. Magnetic fields pass through the different tissues without distortion. The consequence is a better spatial resolution. Third, contrary to EEG, MEG recordings are reference-free.

In event-related experiments, time-locked signals are extracted from the background noise by signal-averaging of data epochs that span each stimulus. Recorded neuromagnetic signals resemble scalp-recorded EEG signals in their appearance. By mathematically modelling of the magnetic field pattern, it is possible to locate the neuronal source and to determine the strength of the recorded signal. Thereby a head-centered coordinate system is used. A problem of source localization is the ‘inverse problem’. This refers to the fact that the scalp recorded magnetic field can have different underlying dipole configurations. To solve this

problem, estimations of the properties of the current sources within the brain have to be made. A prominent technique is the minimum-norm estimation (MNE) (Hämäläinen, 1984; 1994; Hauk, 2004) together with the assumption of a distributed source model. MNE is an inverse method to reconstruct the primary current that underlies an extracranially recorded time-locked magnetic field. The data vector **d** contains the recorded magnetic field strength at measured sensor sites. The leadfield matrix **L** specifies the sensor's sensitivity to the located sources. Further, the vector **j** represents the source current density, and finally **e** represents a noise component. **L** and **d** are known components and **e** is estimated with an accuracy of ~.05. It is assumed that **d** can be described as the product of **L** and **j** plus the noise component (**d = Lj + e**). The MNE algorithm produces an estimate of **j**, which explains most of the data vector **d** and minimizes the sum of the currents **j** with respect to the $\mathbf{l_2}$ minimum-norm method. **j** is estimated by multiplying the pseudo-inverse of the lead-field matrix **L** with the obtained data. The minimum-norm solution for **j** is the only mathematical solution that minimizes the squared current density ($\mathbf{j^2 = min}$). Voltage data in the present study was projected to a source space consisting of 197 evenly distributed dipoles. Thereby a corresponding spherical one-shell brain model with a 6 cm radius is used in the present study.

6.2 Subjects

6.2.1 Experimental group

The experimental group consisted of 18 patients with the DSM-IV diagnosis of PTSD. Due to various artifact sources (see below), neuromagnetic data from 3 subjects were discarded. To ensure that the results of the behavioral data analyses are representative for the subjects whose data entered the neuromagnetic data analyses, the same participants were excluded from the behavioral data analyses. Two additional subjects refused to finish the post-measurement recognition task. Therefore behavioral data of 13 and physiological data of 15 subjects were included in the final analyses. Group mean substitution was used to treat missing data from the two PTSD subjects in the post-test. No systematic differences were found between the excluded and included subjects. In the following, demographics of the

remaining 15 patients are presented. All of these 15 (12 males and 3 females; mean age 31.3 years with a range from 22 to 52, SD = 9.1 years) subjects were Kurdish refugees from Turkey except for one who came from Kosovo. All Kurdish participants were Muslims. Subjects had on average 4.7 (min 0, max 14, SD = 3.8) years of formal education. 14 subjects had only a temporary residence permit status or were in the process of seeking political asylum. 10 subjects were living in asylum facilities, 3 had an own flat and 2 continuously changed their housing. All subjects were outpatients that agreed to participate in a detailed diagnostic exploration and MEG measurement at our Outpatient Clinic for Refugees. 8 of the participants were receiving diverse medication (among most frequently analgesics (N = 5), antidepressants (N = 4), anxiolytics (N = 2) and barbiturates (N = 2)) at the time of testing. No diagnosed neurological disorders were present although it cannot be excluded that some of the subjects might have had some sort of head injury in the past associated with their traumatic experiences. All participants were free from severe somatic illnesses. Because of the very high comorbidity, depression was not considered as an exclusion criterion. A diagnosis of comorbid depression was given in 12 cases. Similarly, prior alcohol abuse (N = 2) was no exclusion criterion. Patients' PTSD symptomatology was evaluated by use of the Posttraumatic Stress Diagnostic Scale (PDS) (Foa, 1995). The traumatic event subjectively evaluated as the most severe was torture (N = 11). All subjects had experienced multiple events. The number of events for a single subject varied between 3 and 6 (see Table 1 for a detailed description of frequency and type of individual traumatic events).

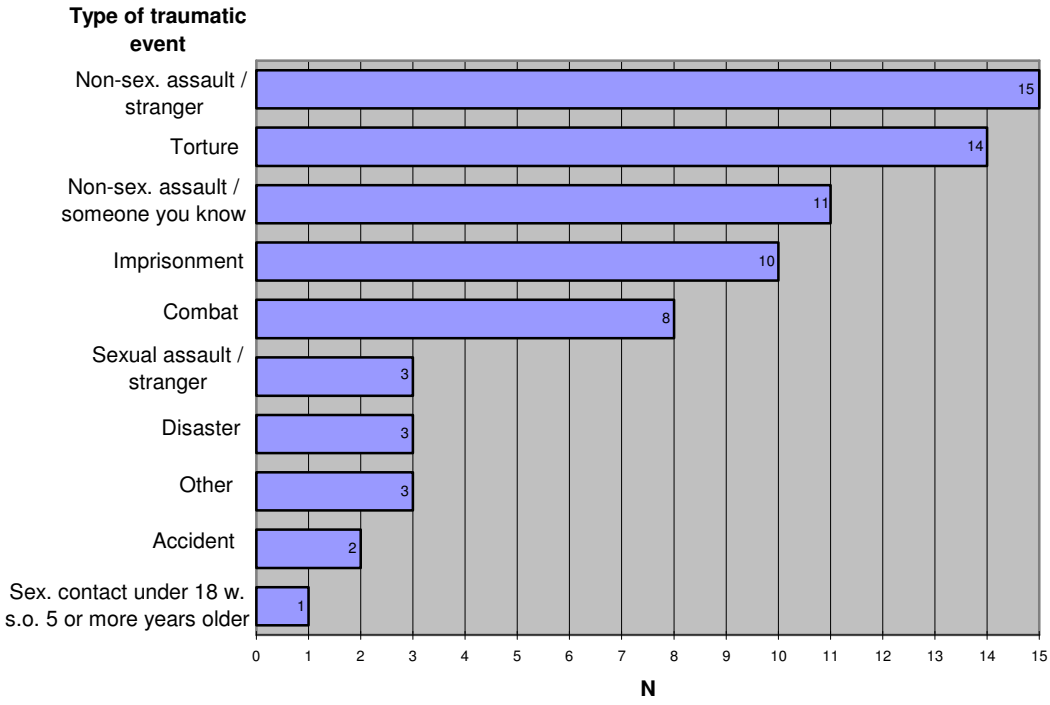


Table 1: Frequency of the different types of traumatic events in the PTSD group (N=15) (multiple nominations possible)

The average overall number of symptoms present at the time of the study was 14.6 (min 10, max 17, SD = 1.6), the mean total symptom severity score was 35.3 (min 22, max 45, SD = 6.6). Symptom severity scores from 21-35 are regarded as 'moderate to severe', higher values as 'severe'. Differentiated mean symptom severity scores were as follows: reexperiencing 10.8 (min 5, max 15, SD = 3.1), avoidance 14.3 (min 9, max 17, SD = 2.5) and arousal 10.3 (min 6, max 15, SD = 2.7). All subjects reported that symptoms influenced all areas of their lifes. An immediate symptoms onset was reported for 13 subjects, a delayed onset for 2 patients. On average the most traumatic event dated back 7.7 years (min 2, max 16, SD = 4.1). A diagnosis of major depression was given by means of ratings in the respective section of the Composite International Diagnostic Interview (CIDI) (WHO, 1997). A total of 12 patients were diagnosed with comorbid depression. Severity ratings were made by means of the Hamilton Depression Scale (HAM-D) (Hamilton, 1960). Overall scores were as follows: average = 46.5 (min = 28, max = 72, SD =

10.9). All participants were right-handed as determined by the Edinburgh Handedness Questionnaire (Oldfield, 1971) and had normal or corrected-to-normal eye vision. Subjects were informed about the goal of the study and gave written consent prior to the experiment.

6.2.2 Control groups

Three different control groups were included in the study:

a.) 28 healthy German control subjects were recruited from colleagues, hospital staff, and advertisements. 7 subjects had to be excluded from the neuromagnetic data analysis because of artifacts (see below). The same subjects were also taken out of the analyses of the post-measurement recognition task for reasons of representativeness. Excluded subjects did not differ systematically from the included ones. Demographics of the remaining 21 participants (13 males and 8 females; mean age 26.2 years, SD = 5.5 years) are given. All subjects grew up with a Christian background. Average years of formal education were 15.5 (min 12, max 20, SD = 2.5). Subjects were screened for present psychological, neurological, and somatic disorders and were excluded if any of these were apparent. The German version of the Beck-Depression-Inventory (BDI) (Hautzinger, 1994) and the State-Trait Anxiety Inventory (STAI) (Spielberger, 1983) were administered. The average BDI score was 3.7 (min = 0, max = 9, SD = 2.9). BDI values higher than 12 are regarded as clinically relevant. The average STAI-trait score was 34.5 (min = 24, max = 63, SD = 8.2), the average STAI-state score was 35.7 (min = 26, max = 45, SD = 4.3). For a comparison: in a normative sample of students (N = 216) the following scores were found: STAI-trait: M = 40.5, SD = 9.1, STAI-state: M = 37.9, SD = 9.1 (taken from the German version of the Stait-Trait Anxiety Inventory, Laux, 1981). Only one subject had a slightly heightened trait anxiety score compared to the normative sample but was otherwise evaluated as psychologically normal. Participants had no history of substance abuse and were free of medication.

b.) To account for cultural / religious differences an own Muslim Kurdish control group was recruited (N = 12). Two subjects had to be excluded from the

neuromagnetic data analyses (for reasons see below). The same 10 remaining subjects entered the behavioral data analyses. Excluded subjects did not differ systematically from the included ones. In the following, demographic information of the 10 (5 males and 5 females; mean age 28.3 years with a range from 21 to 40, SD = 6.0 years) subjects included in the further data analyses are presented. Subjects in this group had a mean of 4.4 (min 0, max 10, SD = 3.7) years of formal education. In contrast to the experimental group participants in this group had an unlimited or at least prolongable residence permit status and lived in an own flat. To evaluate the psychological, neurological, and somatic integrity, a shortened version of the same diagnostic procedure as the experimental group went through was completed. None of the subjects had a diagnosis of PTSD, although 9 reported traumatic events. Particularly residence in an operational war zone was prominent (N = 6). 5 subjects reported multiple (2 or 3) events (see Table 2 for a detailed overview of frequency and type of individual traumatic events).

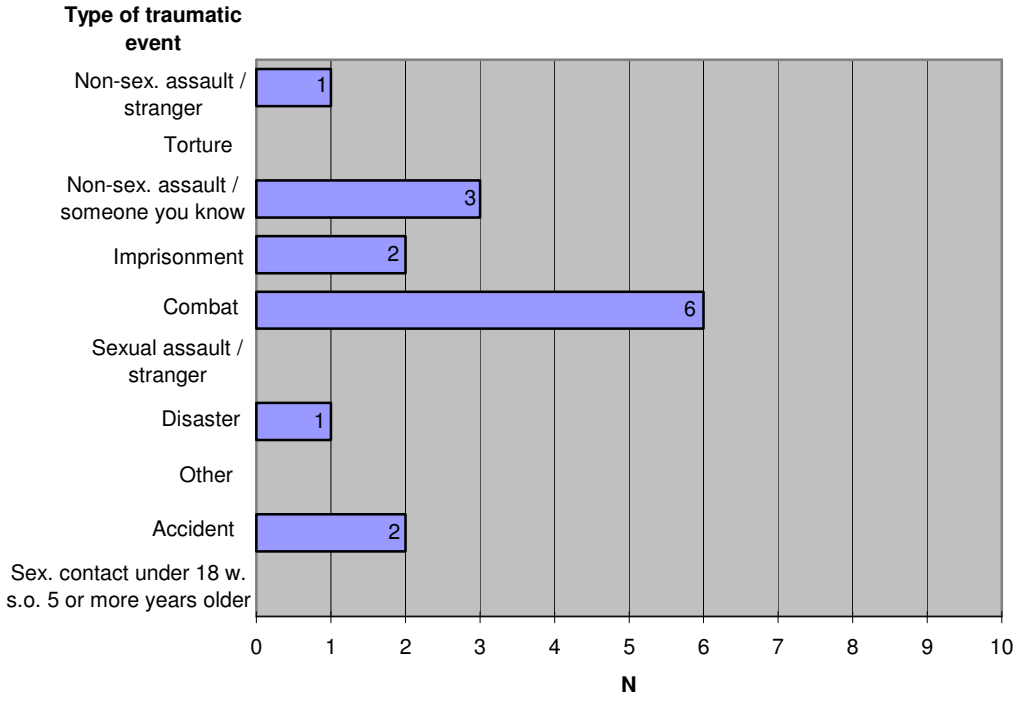


Table 2: Frequency of the different types of traumatic events in the Kurdish control group (N=10) (multiple nominations possible)

On average the most distressing event had happened 11.8 (min 3, max 23, SD = 5.2) years ago. No subject reported PTSD related symptoms. Likewise, absence of any other psychological, neurological, or somatic disorders was made sure. Only one subject reported significant symptoms of mild depression. The average HAM-D score was 8.4 (min = 0, max = 26, SD = 8.9). Participants had no prior substance or alcohol abuse and were free of any medication.

c.) A clinical control group of 26 DSM-IV diagnosed schizophrenia patients was recruited. Just like in the other groups, 5 neuromagnetic data sets had to be discarded for artifact reasons (see below). Behavioral data of these subjects were also excluded for reasons of representativeness. No systematic differences were found between included and excluded participants. Demographics of the remaining 21 (17 males and 4 females; mean age 30.5 years with a range from 19 to 49, SD = 8.6 years) patients are given. All subjects had a Christian background and on average 12.0 years of formal education (min 9, max 18, SD = 3.0). At the time of the investigation patients were inpatients at a state psychiatric hospital and had been diagnosed by a psychiatrist or clinical psychologist. All subjects were diagnosed with a paranoid schizophrenia. Only one patient was included who met the criteria for a schizophreniform disorder. All patients were treated with neuroleptic medication at the time of testing. The mean chlorpromazine equivalent was 594.5 mg/day (SD = 270.7, min = 105.0, max 1200.0). The chlorpromazin equivalent was calculated using the method described by Jahn (1989). 3 subjects additionally received anxiolytics and 2 a phase prophylactic medication. All participants were free of neurological or severe somatic disorders. Cannabis abuse was present in 6 subjects, alcohol abuse in history in 2 patients. On the day of the MEG-measurement the following diagnostic scales were used by the patient's therapist to assess the present clinical symptoms: Positive and Negative Syndrome Scale (PANSS) (Kay, 1987), the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1981) and the Brief Psychiatric Rating Scale (BPRS) (Overall, 1962, as modified by Lukoff, 1986). The average PANSS-P score was 13.8 (min 7, max 24, SD = 4.9), PANSS-N was 21.9 (min 7, max 36, SD = 7.4) and PANSS-G was 32.9 (min 24, max 49, SD = 6.4). The SANS overall scores varied between 16 and

88 (M = 53.1, SD = 21.4) and the mean BPRS score was 41.8 (min 28, max 65, SD = 7.9). According to the DSM-IV axis V, global functioning was assessed applying the Global Assessment of Functioning Scale (GAF). The average score was 38.9 (SD = 10.0) and varied between 28 and 65.

All control subjects were right-handed and had normal or corrected-to-normal eye vision. Informed consent was given prior to the investigation and they received a financial bonus for their participation.

6.2.3 Comparisons between groups and summary

Comparisons between the four groups did not show significant differences in age ((F(3,63) = 1.7, p > .05)) but they differed significantly in their level of education ((F(3,63) = 48.0, p < .005)). Post hoc tests (HSD; α = .05) revealed that the healthy German control group had a significantly higher formal education level than all other groups, followed by the Schizophrenic subjects. The PTSD and Kurdish control group did not differ from each other. An overview of demographic information and results of the clinical questionnaires for all four groups can be seen in Tables 3 and 4.

In the following, the four groups are referred to as PTSD (PTSD patients), C (German controls), K (Kurdish controls) and SZ (Schizophrenic patients).

Table 3: Demographics (Values of subjects whose neuromagnetic data were analyzed are given; numbers in parentheses display values of the total samples)

	PTSD	**Controls (German)**	**Controls (Kurdish)**	**Controls (Schizophrenics)**
N	15 (18)	21 (28)	10 (12)	21 (26)
Sex				
males [N]	12 (15)	13 (18)	5 (7)	17 (19)
females [N]	3 (3)	8 (10)	5 (5)	4 (7)
Age [M / SD]	31.3 / 9.1 (31.3 / 8.5)	26.2 / 5.5 (27.0 / 6.5)	28.3 / 6.0 (28.6 / 5.5)	30.5 / 8.6 (29.7 / 8.7)
Ethnicity				
Kurdish [N]	14 (15)	0 (0)	10 (12)	0 (0)
German [N]	0 (0)	21 (28)	0 (0)	21 (26)
Other [N]	1 (3)	0 (0)	0 (0)	0 (0)
Educat. (years) [M / SD]	4.7 / 3.8 (5.4 / 4.6)	15.5 / 2.5 (16.0 / 2.5)	4.4 / 3.7 (4.8 / 3.6)	12.0 / 3.0 (11.8 / 2.8)
Alcohol abuse [N]	2 (2)	0 (0)	0 (1)	2 (2)
THC abuse [N]	0 (0)	0 (0)	0 (1)	6 (6)
(comorbid) Depress. [N]	12 (14)	0 (0)	1 (2)	0 (0)

Table 4: Clinical questionnaires (Values of subjects whose neuromagnetic data were analyzed are given; numbers in parentheses display values of the total samples)

	PTSD			Controls (German)			Controls (Kurdish)			Controls (Schizophrenics)		
	M	**SD**	**Range**	**M**	**SD**	**Range**	**M**	**SD**	**Range**	**M**	**SD**	**Range**
PDS												
no. of events	4.7 (4.6)	1.2 (1.3)	3-6 (2-6)	-	-	-	1.5 (1.8)	0.8 (1.1)	0-3 (0-4)	-	-	-
tot. no. of symp.	14.6 (14.3)	1.6 (2.0)	10-17 (10-17)	-	-	-	n.a.	n.a.	n.a.	-	-	-
tot. sympt. sev.	35.3 (34.8)	6.6 (7.5)	22-45 (18-45)	-	-	-	n.a.	n.a.	n.a.	-	-	-
reexp. sev. sc.	10.8 (10.8)	3.1 (2.8)	5-15 (5-15)	-	-	-	n.a.	n.a.	n.a.	-	-	-
avoid. sev. sc.	14.3 (14.0)	2.5 (3.5)	9-17 (4-18)	-	-	-	n.a.	n.a.	n.a.	-	-	-
arousal sev. sc.	10.3 (10.0)	2.7 (2.9)	6-15 (4-15)	-	-	-	n.a.	n.a.	n.a.	-	-	-
sympt. dur. (yrs)	7.7 (7.4)	4.1 (4.2)	2-16 (2-16)	-	-	-	n.a.	n.a.	n.a.	-	-	-
delayed onset	N = 2 (3)			-	-	-	n.a.	n.a.	n.a.	-	-	-
HAM-D score	46.5 (45.1)	10.9 (11.0)	28-72 (26-72)	-	-	-	8.4 (9.3)	8.9 (10.2)	0-26 (0-28)	-	-	-
BDI score	-	-	-	3.7 (3.2)	2.9 (2.7)	0-9 (0-9)	-	-	-	-	-	-
STAI												
state score	-	-	-	35.7 (33.9)	4.3 (5.0)	26-45 (25-45)	-	-	-	-	-	-
trait score	-	-	-	34.5 (33.1)	8.2 (7.6)	24-63 (24-63)	-	-	-	-	-	-
PANSS												
pos. sympt. sc.	-	-	-	-	-	-	-	-	-	13.8 (13.2)	4.9 (4.8)	7-24 (7-24)
neg. sympt. sc.	-	-	-	-	-	-	-	-	-	21.9 (21.3)	7.4 (6.9)	7-36 (7-36)
gen. sympt. sc.	-	-	-	-	-	-	-	-	-	32.9 (32.5)	6.4 (6.1)	24-49 (24-49)
SANS score	-	-	-	-	-	-	-	-	-	53.1 (52.7)	21.4 (22.0)	16-88 (7-88)
BPRS score	-	-	-	-	-	-	-	-	-	41.8 (40.9)	7.9 (7.5)	28-65 (28-65)
GAF score	-	-	-	-	-	-	-	-	-	38.9 (39.9)	10.0 (10.1)	28-65 (28-65)

6.3 Stimuli

288 colored photographs were used as stimuli consisting of 96 pleasant, 96 unpleasant and 96 neutral pictures. About half of the pictures were selected from the IAPS (international affective picture system; Lang, 1999) (pleasant N = 39, unpleasant N = 53, neutral N = 37) and the existent normative valence and arousal ratings for these pictures were used. In addition 159 pictures were collected from diverse internet sites and were rated by 32 subjects (16 females and 16 males; mean age 26.8 years with a range from 18 to 47, SD = 4.9 years) on the two dimensions pleasure and arousal using a computerized version of the Self-Assessment Manikin (SAM; Lang, 1980). On this language-free rating instrument subjects rate the dimensions pleasure and arousal on two nine-level graphic figure scales (pleasure scale: level 1 meaning 'most unpleasant', level 5 meaning 'neutral', level 9 meaning 'most pleasant'; arousal scale: level 1 meaning 'relaxed' and level 9 meaning 'highest arousal'). Subjects were screened for depressive and anxiety symptoms using the BDI (M = 2.3, min = 0, max = 10, SD = 3.0; scores higher than 12 are regarded as clinically relevant) and STAI (state version: M = 32.9, min = 23, max = 54, SD = 6.7; trait version: M = 31.9, min = 21, max = 52, SD = 7.7) questionnaires. No clinically significant symptoms were found. Only one subject had slightly higher anxiety scores than a normative sample of students (N = 216, STAI-trait: M = 40.5, SD = 9.1, STAI-state: M = 37.9, SD = 9.1) (Laux, 1981). All subjects had a Christian background.

Pleasant pictures included erotic couples (N = 14), nudes of both sexes (males N = 7, females N = 8), happy families (N = 20) and children (N = 12), cute animals (N = 8), sport pictures (N = 24), and other (N = 3). Unpleasant pictures included scenes of attack and threat (N = 33), mutilated bodies (N = 15), fierce animals (N = 5), scenes of accidents (N = 3), wounded persons (N = 10), sorrowing persons (N = 12), disgusting or threatening objects (N = 5), and other pictures of grief (N = 13). Neutral pictures included neutral faces (N = 25), neutral social interactions or activities (N = 60), animals (N = 5), and pictures of landscapes or buildings (N = 6).

Most studies investigating the processing of emotional visual stimuli used pictures of non-living objects as neutral pictures, whereas pleasant and unpleasant pictures mainly depicted humans. Since we propose a general difference in the processing of social cues versus non-living objects, we matched all three categories of pictures according to the display of social content. Therefore 83 of pleasant, 84 of

unpleasant, and 85 of neutral pictures showed humans / social content. The three categories further included 6, 7, and 6 pictures of non-living objects / situations not depicting humans respectively. In addition 7 pleasant, 5 unpleasant, and 5 neutral pictures of animals were included. All pictures were matched for size, contrast, and brightness.

2-way ANOVAs (dependent variable: 'Valence' or 'Arousal', independent variable: picture 'Category', between-groups factor: 'Sex') were calculated to compare valence and arousal scores and to investigate possible gender effects. Normative picture ratings of valence differed as a function of picture category ($F(2,570) = 1480.3$, $p < .001$). Pleasant ($M = 6.65$, $SD = .88$), unpleasant: ($M = 2.62$, $SD = .78$) and neutral pictures ($M = 5.08$, $SD = .57$) were all rated as significantly different from each other.

A significant Category x Sex interaction ($F(2,570) = 12.78$, $p < .001$) and later post-hoc comparisons (HSD; $\alpha = .05$) revealed that females ($M = 2.3$, $SD = .66$) rated unpleasant pictures as more unpleasant than males ($M = 2.94$, $SD = .75$).

Similar to valence, arousal ratings also differed as a function of picture category ($F(2,570) = 468.28$, $p < .001$). Unpleasant pictures had the highest arousal scores ($M = 5.94$, $SD = .86$), followed by pleasant ($M = 4.87$, $SD = 1.31$) and neutral ($M = 2.86$, $SD = 0.81$) pictures.

A significant Category x Sex interaction ($F(2,570) = 10.0$, $p < .001$) and later post-hoc comparisons (HSD; $\alpha = .05$) revealed that females ($M = 6.28$, $SD = .76$) rated unpleasant pictures as more arousing than males ($M = 5.6$, $SD = .82$).

Figure 8 shows correlations between valence and arousal ratings for the complete subject sample together with the two motivational gradients (appetitive and defensive).

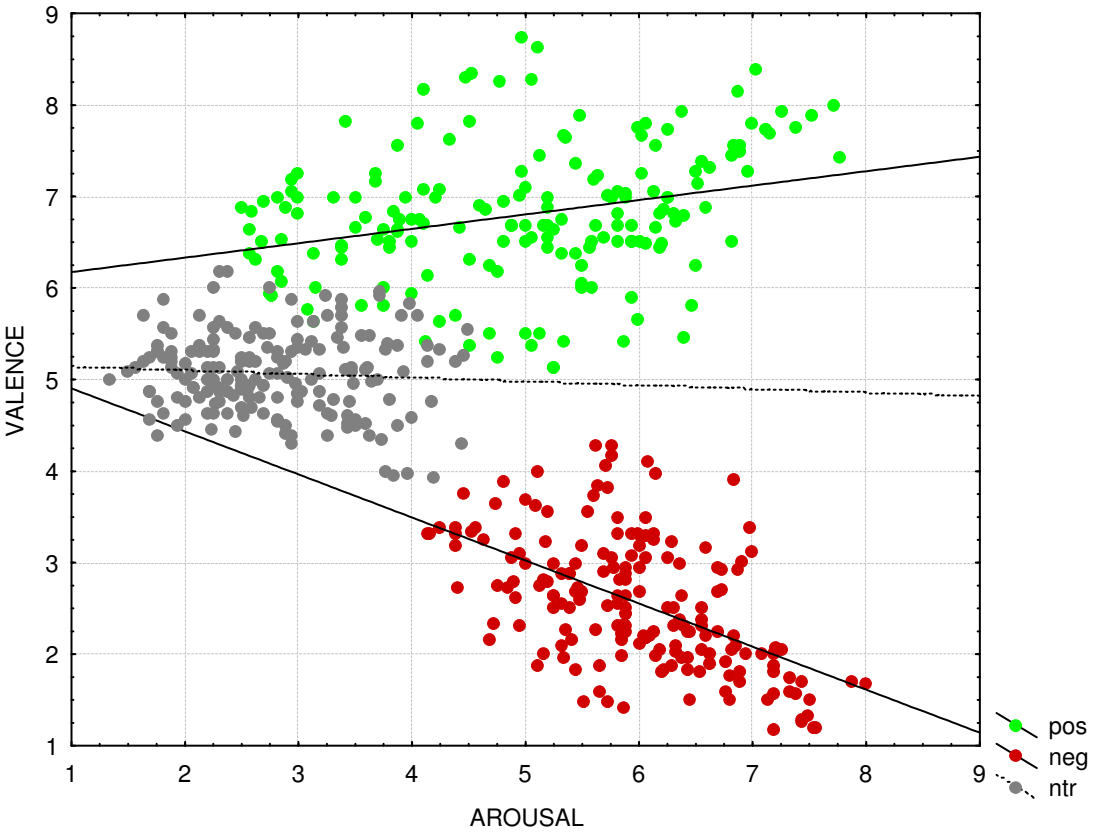


Figure 8: Correlations between VALENCE and AROUSAL ratings for the three picture categories.

6.4 Experimental Design

6.4.1 MEG-measurement

After attaching MEG-coils and EOG and ECG electrodes, subjects were accompanied to the sound attenuated and dimly lit MEG-chamber. The experiment took place in a supine position. The experiment began with a 5min baseline resting period. Subjects were told not to move, to blink as rarely as possible, and to fixate a small colored dot on the ceiling above them to avoid eye movements. Results of this baseline measurement are not reported here. Afterwards, subjects were instructed to attentively watch the pictures that appeared above them via a video beamer projection. The software running the experimental paradigm was 'PRESENTATION', a stimulus delivery and experimental control software system for neuroscience

developed by Neurobehavioral Systems (NBS®). This software provides very good timing accuracy and timing verification.

The subsequent main paradigm was divided into three measurement runs to minimize the strain of the subjects in terms of discomfort due to the required motionlessness. Runs were divided by a short pause in which subjects were allowed to move their limbs and close their eyes for a brief period of time. Subjects were also asked if they feel comfortable. Pauses lasted not longer than 5min in general.
Run 1 and 2 form an entity since run 2 was just a continuation of run 1. Again, subjects were instructed not to move and to blink as rarely as possible. Furthermore, they were told to watch the following slides attentively and to try to keep as many of them in memory as possible.

After a four second visual number countdown the experimental stimuli appeared in the following manner: pictures were organized in blocks of six slides, containing two randomly picked pictures from each category respectively. Each block was immediately repeated after its first presentation, maintaining the previous order of slides. After this repetition a new block was started not including any of the previously shown slides. There was no delay between blocks so that the whole presentation was a continuous stream of slides. Across subjects, blocks of slides were always randomly composed so that each subject saw an individual stream of pictures. Run 3 differed from runs 1 and 2 since it was a single repetition of all 288 pictures in the order in which slides were shown in the previous two runs. Therefore, approximately 10.8s elapsed between the first and second viewing of each picture and approximately 28min between the second and third presentation.
Each picture was presented for 1200ms with a fixed interstimulus interval (ISI) of 600ms. During the ISI a small white fixation cross on a black background was displayed.

6.4.2 Recognition task

After the MEG-measurement coils and electrodes were removed and the subjects were told that they now had to do a brief post recognition test. Subjects sat in front of a computer screen and were told that the investigator would show again some of the pictures to them used during the MEG-measurement. In addition, they would see

some slides that they had not previously seen. Subjects were instructed to answer with ‘yes’, if they believed that they had seen a picture earlier and to respond with ’no’, if they believed that a picture was new. A total of 72 pictures randomly picked from the overall set of the 288 pictures was used. The only fixed criterion was that an equal amount of pictures was taken from each category. Same was true for distractor items. These slides were presented in mixed random order together with a total of 72 additional distractor slides. The distractors were randomly picked from a separate picture set of 288 pictures that were matched in all qualities to the original slide set.

Stimulus presentation time during the recognition task was 1500ms. In contrast to the MEG-experiment the duration of the ISI was dependent on the subjects answer. The investigator pressed one of two mouse buttons according to the subjects answers ’yes’ or ’no’. The button press was the impulse for the presentation of the next picture. Target pictures were preceded by three probe pictures so that subjects could get familiar to the procedure. These three items were excluded from the analysis.

6.5 MEG data recording and data reduction

The MEG measurements were done using a 148-channel magnetometer (MAGNES™ 2500 WH, 4D Neuroimaging, San Diego, USA). Neuromagnetic data was continuously recorded with a sampling rate of 678.17 Hz and a bandpass filter of 0.1 (high-pass) to 100 (low-pass) Hz.

To control for blink artifacts, the electrooculogram (EOG) was recorded from four electrodes placed at the left and right temporal canthus and above and below the right eye. Furthermore, heart rate was derived from the electrocardiogram (ECG) that was recorded from two electrodes attached to the right and left forearm respectively. EOG and ECG recordings were provided by a SynAmps amplifier (NEUROSCAN). Individual head shape information was acquired before the recording session. Before and after the session measurements were done of the sensor array position in relation to the individual head coordinate system.

After the MEG measurements the data were noise reduced and corrected for cardiac activity and for eye blinks. Data epochs with a post-trigger duration of 1200ms and a 100ms pre-trigger baseline period were analyzed. Data sets

underwent an automated artifact scan after a gross manual inspection. In case of defect sensors, these channels were interpolated. Epochs including artifacts (the threshold for peak-to-peak amplitude in the MEG channels was set to 3.5 pT) were excluded from further analyses. Altogether 17 subjects had to be rejected from the final analyses for the following reasons: continuous head movements during the recording period (N = 5), high ratio of blink-contaminated compared to blink-free trials (N = 5), frequently occurring Alpha-wave activity as an indicator of sleepiness (N = 4), contamination of the MEG signal by presence of electroconductive metal implants (N = 2), epileptic activity (N = 1). Overall the least number of accepted trials for the remaining 67 subjects was on average 86 (SD = 6) per condition. These trials were averaged and filtered with a 1 Hz (6 dB/oct, forward shift) high-pass and a 40 Hz (12 dB/oct, zero phase shift) low-pass filter. Preprocessing was done using BESA® software (MEGIS Software GmbH).

Customized Matlab® based software (EMEGS©) was used to calculate minimum norm solutions for each of the averaged files. For this purpose the data were downsampled to 250 Hz. A spherical one shell (6 cm radius) solution was applied. Individual head shape information was used for single-subject calculations.

For the statistical analyses the data were logarithmized (log10).

6.6 Statistical analyses

6.6.1 Neuromagnetic data

Comparisons of means were made using 4-way repeated measures analysis of variance (ANOVA) with the three within-subject factors picture 'Category' (3 levels: neg, pos, ntr), presentation point in 'Time' (3 levels: first, second, third presentation) and 'Hemisphere' (2 levels: right, left). 'Group' (4 levels: PTSD, C, K, SZ) was added to the ANOVA as the between-groups (categorical) factor. The Greenhouse / Geisser epsilon correction procedure was applied to account for possible violations of the homogeneity of variance assumption. Adjusted p-values are reported. If ANOVAs revealed significant main effects or interactions, Fisher's least significant difference (LSD) test was applied for post-hoc comparisons. The α-level was set at .05 for all comparisons. A statistical trend-level was defined for p-values between .05 and 0.1.

6.6.2 Behavioral data

To compare subjects' performance on the post-measurement recognition task, the following parameters were calculated for each of the picture categories and each group separately: hit rate, false alarm rate. These two variables were then used to calculate d prime (d') and the criterion (C). d' is a measure of sensitivity derived from Signal Detection Theory. It is the standardized difference between the means of the Signal Present and Signal Absent distributions.The formula for d' is as follows:

$$\mathbf{d' = z\,(H) - z\,(FA)}$$

where z (H) and z (FA) represent the conversion of the hit and false alarm rates to z-scores. A common z table can been used to perform the conversion. Larger values of d' mean that a person is better at differentiating between the Signal Present and Signal Absent distributions (in this case differentiating between 'old' and 'new' pictures of a category). Further details about signal detection measures and d' can be found in Wickens (2001). The same author also provides a d' calculator software.

C is a measure used for evaluation of possible response biases. It represents the minimum level of internal certainty a subject needs to make his/her decision that a signal was present. C is calculated using the following formula:

$$\mathbf{C = -\,[z\,(H) + z\,(FA)]\,/\,2}$$

A criterion of zero means that the subject is unbiased. If C > 0 the subject uses a stricter criterion, if C < 0 the subject is biased in favour of saying 'old'.

d' and C were both calculated for each picture category separately. In addition a total score was computed for both measures.

Group mean substitution was applied in the two cases of missing data in the PTSD group.

Comparisons of means were then made by 2-way repeated measures ANOVAs (within-subject factor picture 'Category' with the 3 levels neg, pos, ntr; between-groups factor 'Group' with the 4 levels: PTSD, C, K, SZ). Greenhouse /

Geisser-corrected p-values are reported. The LSD test was applied for post-hoc comparisons with an α-level of .05.

6.6.3 Psychopathology and neuromagnetic parameters

Product-moment correlations as well as multiple regression analyses were calculated between selected psychopathology / demographic characteristics and designated parameters derived from the neuromagnetic data analyses. This was done to get insight into the predictive importance of certain pathological symptoms for the brain response. Pearson's r was computed to see the strength of the correlation with the dependent variable. Correlations of below .25 were regarded as ‘low’, .25 to .50 as ’medium’, .50 to .75 as ’high’, and .75 to 1.0 as ’complete’. In the regression analyses, R^2 represents the joint contributions of all independent variables in the chosen model to the explanation of variance of the dependent variable. It is the percent of the variance in the dependent explained jointly by the independents. Beta weights reflect the unique contribution of each independent variable.

7 Results

7.1 Behavioral data - recognition performance and response biases

To investigate how groups differed in their recognition performance a 2-way repeated measures ANOVA for d' was calculated. The Category x Group interaction was significant ($F(6,126) = 2.21$; $p < .048$; $\varepsilon = .975$). Post hoc tests revealed that all groups performed similarly well on recognizing negative target pictures. For this picture category no differences were found across groups. Further, the three control groups showed similar recognition performance for all three picture categories. Strikingly, the PTSD group was characterized by poor performance for the positive pictures. Whereas d' had a value of 2.5 for the negative slides, it was only 1.6 for the positive ones ($p < .001$). The performance for neutral stimuli laid between the two other categories with a d' of 2.1 (see Figure 9). Overall, the PTSD group showed a similarly high recognition performance like the other three groups for negative pictures. Recognition for positive slides was worst. Performance for neutral images was better than for positive, but worse than for negative ones.

In addition a significant Group main effect ($F(3,63) = 6.05$; $p < .002$) demonstrated the best overall performance in the healthy German controls followed by the Schizophrenic group.

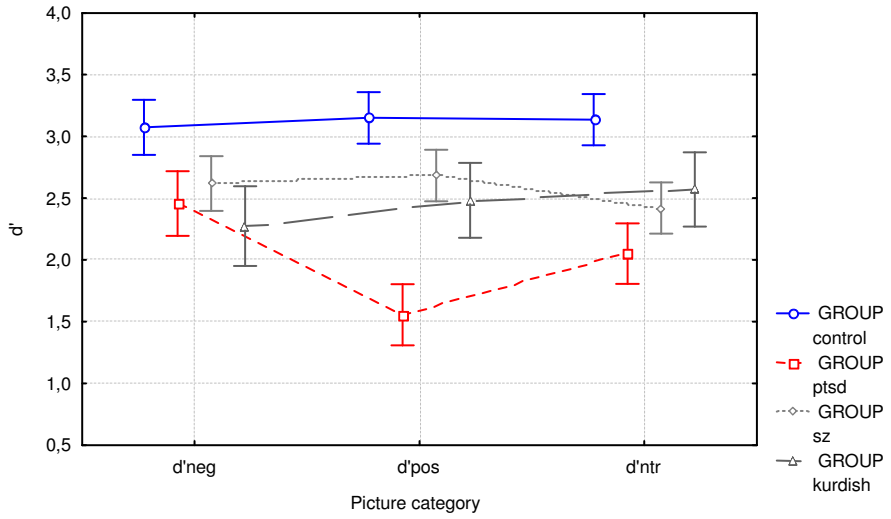


Figure 9: Category x Group interaction for d'. PTSD subjects show preserved recognition performance for aversive pictures only. For this picture category PTSD patients do not differ significantly from the control groups. However, performance is significantly impaired for positive and neutral material.

To analyze possible response biases, a 2-way repeated measures ANOVA for the criterion C was calculated. A significant Category main effect ($F(2,126) = 41.72$; $p < .001$; $\varepsilon = .95$) and subsequent post hoc tests showed a graded value for C. Across all four groups C was highest for neutral pictures, followed by positive and again followed by negative pictures (ntr vs pos: $p < .001$; ntr vs neg: $p < .001$; pos vs neg: $p < .002$) (see Figure 10). This means that all subjects were least certain that they had seen the neutral target slides before. They were more willing to say that they had not seen a neutral target before. On the other hand all subjects were relatively confident in keeping apart negative target and distractor slides.

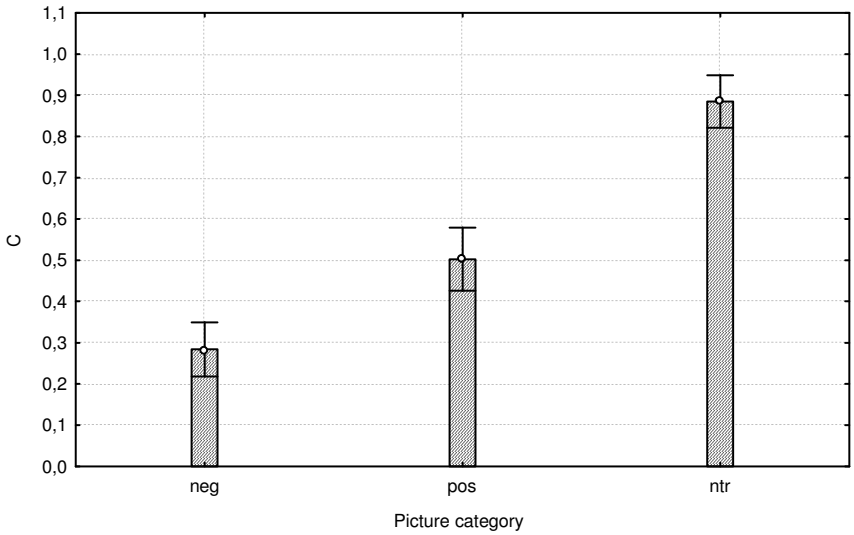


Figure 10: Category main effect for C. Subjects from all groups were least certain that they had seen the neutral target slides before. They were most certain in discriminating negative pictures.

Table 5 shows the decision matrix for each group and each picture category, as well as for the total score. Included are hits, false alarms, misses, and correct rejections. In addition the empirical values for d' and C are displayed.

	C (n=21)			PTSD (n=15)			SZ (n=21)			K (n=10)		
	Neg											
	M	SD	RG	M	SD	RG	M	SD	RG	M	SD	RG
Hits	20.4	2.9	13-24	20.2	2.2	17-24	18.7	4.4	5-24	17.8	3.7	12-23
False Alarm	1.6	1,7	0-7	3.7	3.5	0-12	2.0	1.8	0-6	2.7	2.5	0-7
Misses	3.6	2.9	0-11	3.8	2.2	0-7	5.3	4.4	0-19	6.2	3.7	1-12
Corr. reject.	22.4	1.7	17-24	20.3	3.5	12-24	22.0	1.8	18-24	21.3	2.5	17-24
d’	3.1	0.8	1.6-4.7	2.5	0.9	1.4-4.7	2.6	1.2	0.3-4.7	2.3	1.1	1.1-4.0
C	0.3	0.6	-0.8-1.3	0	0.5	-0.7-1.2	0.4	0.5	-0.6-1.3	0.4	0.5	-0.2-1.0
	Pos											
	M	SD	RG	M	SD	RG	M	SD	RG	M	SD	RG
Hits	20.6	2.0	17-24	13.9	3.5	9-22	18.0	3.6	11-23	17.6	3.7	10-22
False Alarm	1.6	1.8	0-6	3.7	3.8	0-16	1.9	2.9	0-12	2.9	4.9	0-16
Misses	3.4	2.0	0-7	10.1	3.5	2-15	6.0	3.6	1-13	6.4	3.7	2-14
Corr. reject.	22.4	1.8	18-24	20.3	3.8	8-24	22.1	2.9	12-24	21.1	4.9	8-24
d’	3.2	0.9	1.6-4.4	1.6	0.8	0.2-3.2	2.7	1.0	0.8-4.7	2.5	1.1	0.5-4.0
C	0.3	0.6	-1.1-1.2	0.5	0.5	-0.6-1.5	0.6	0.6	-0.5-1.5	0.6	0.7	-0.7-1.4
	Ntr											
	M	SD	RG	M	SD	RG	M	SD	RG	M	SD	RG
Hits	19.4	2.2	15-23	13.1	3.9	4-18	13.9	4.4	8-22	13.9	5.5	8-21
False Alarm	1.0	1.1	0-3	1.7	1.6	0-5	1.1	1.8	0-7	1.0	1.5	0-4
Misses	4.6	2.2	1-9	10.9	3.9	6-20	10.1	4.4	2-16	10.1	5.5	3-16
Corr. reject.	23.0	1.1	21-24	22.3	1.6	19-24	22.9	1.8	17-24	23.0	1.5	20-24
d’	3.1	0.9	1.6-4.7	2.1	0.7	0.7-3.2	2.4	1.0	0.7-4.0	2.6	1.2	0.5-4.0
C	0.6	0.4	-0.1-1.3	0.9	0.6	0.1-2.0	1.0	0.5	0.1-1.7	1.0	0.5	0.3-1.7
	Total											
	M	SD	RG	M	SD	RG	M	SD	RG	M	SD	RG
Hits	60.4	6.0	48-70	47.2	7.6	34-61	50.5	10.4	27-69	49.3	11.8	30-65
False Alarm	4.1	3.3	0-12	9.0	7.7	0-33	5.0	5.8	0-25	6.6	8.3	0-27
Misses	11.6	6.0	2-24	24.8	7.6	11-38	21.5	10.4	3-45	22.7	11.8	7-42
Corr. reject.	67.9	3.3	60-72	63.0	7.7	39-72	67.0	5.8	47-72	65.4	8.3	45-72
d’	2.8	0.6	1.9-4.2	1.8	0.5	0.8-3.2	2.3	0.9	1.0-4.1	2.2	1.1	0.6-4.0
C	0.3	0.4	-0.2-1.1	0.5	0.4	-0.3-1.4	0.6	0.4	-0.2-1.2	0.6	0.4	0-1.1

Table 5: Decision matrix for the post-measurement recognition task.

7.2 Neuromagnetic data

7.2.1 Selection of time intervals and ROI

Visual inspection of the Global Field Power calculated for each group and each experimental condition led to the selection of the following time windows that covered the full range of the ERP effects within the 1200ms time interval: 90-120, 120-180, 230-380, 380-600 and 600-720ms. For the time intervals from 120-180 and 600-720ms various analyses including several functional ROI led only to unsystematic effects and are therefore not further addressed. An example of a Global Power plot can be seen in Figure 11. The magnetic field strength in response to the first and third presentation of negative pictures in the Control group is shown. Other conditions resulted in similar plots.

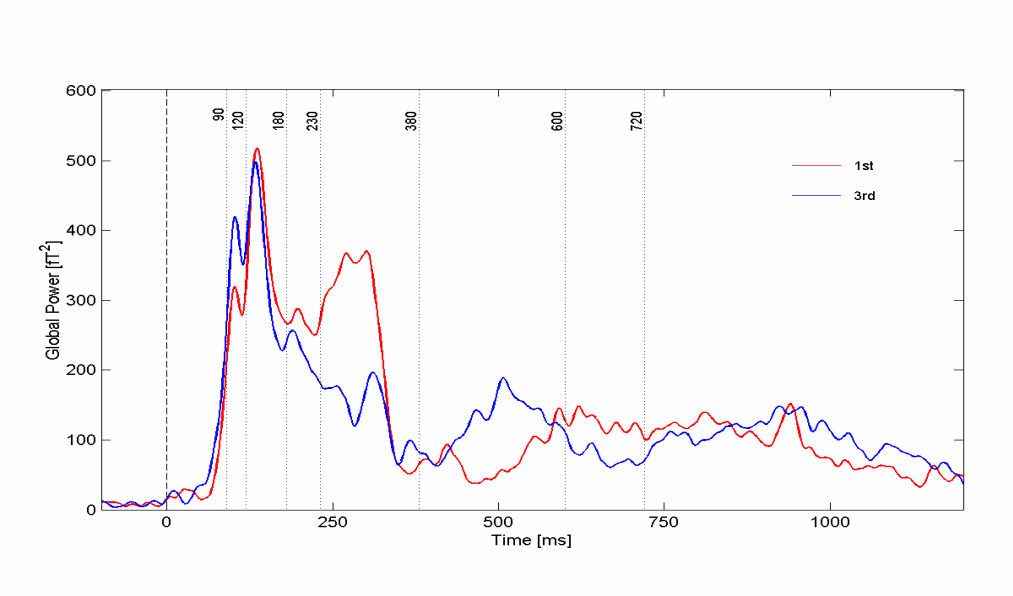


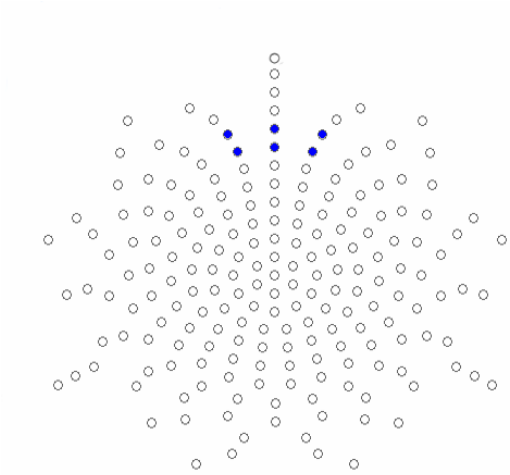
Figure 11: Example of a Grand Mean Global Power [fT^2] plot of the magnetic field strength (here 1st and 3nd presentation of negative pictures in the Control group). Time intervals used for the Minimum Norm estimations were selected by visual inspection of the Global Power.

In correspondence to the theoretical background, gross brain regions that are regarded as crucial for certain cognitive functions like object recognition or memory were investigated. The respective final dipole groups (regions of interest; ROI) that were used for Minimum Norm calculations were selected where significant differences in signal amplitude between conditions and groups were found. These dipole groups are listed in Table 6 and shown in Figures 12 a-d.

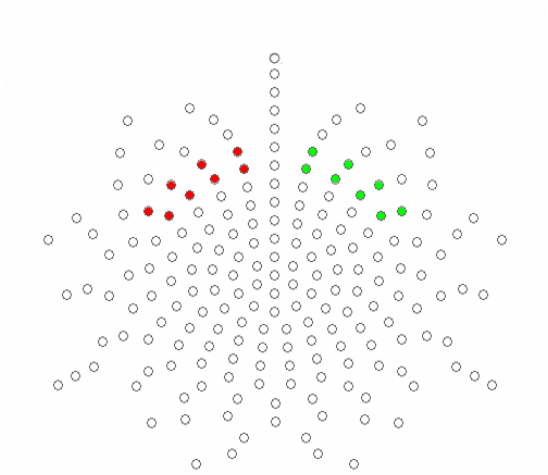
	dipole numbers	
	right hemisphere	**left hemisphere**
orbitofrontal, 90-120ms	81-82, 105-108, 128-132, 150-151	
inferior frontal, 230-380ms	102-105, 126-129	82-85, 107-110
anterior temporal 230-380ms	100-101, 124-125, 146-148, 166-167	86-87, 111-112, 134-136, 156-157
temporal, 380-600ms	98-102, 122-126, 145-148	85-89, 110-114, 134-137

Table 6: ROI; dipole numbers.

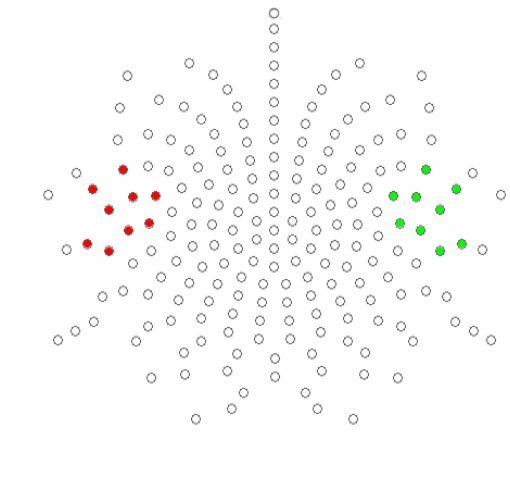
a.) orbitofrontal regions, time interval 90-120ms



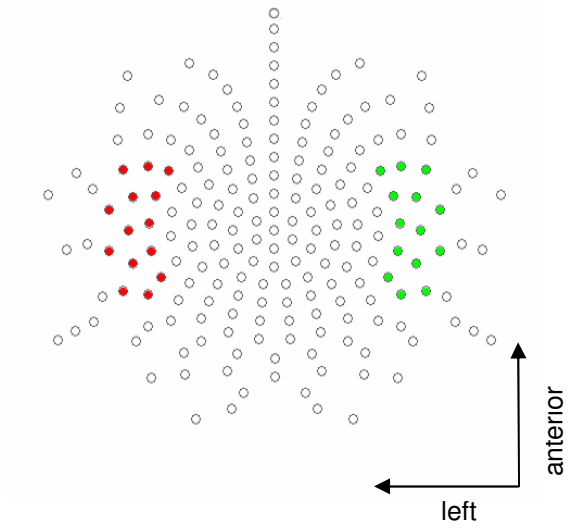
b.) inf. frontal regions, time interval 230-380ms



c.) ant. temp. reg., time interval 230-380ms



d.) temporal regions, time interval 380-600ms



Figures 12 a-d: Dipole groups used for data analysis (green and red colors represent selected dipoles in the right and left hemisphere respectively; blue color represents non-lateralized ROI).

7.2.2 Orbitofrontal regions (90-120ms)

A 4-way repeated measures ANOVA (within-subject factors Category, Time, Hemisphere; between-groups factor Group) did not yield any significant results ($F(12,252) = 1.01$; $p < .443$; $\varepsilon = .935$). However, from visual inspection of the interaction plot (see Figure 13) it is obvious that the PTSD group shows extraordinarily high amplitudes in response to the first presentation of negative pictures. This observation is in line with a study from Junghoefer et al. (2003).

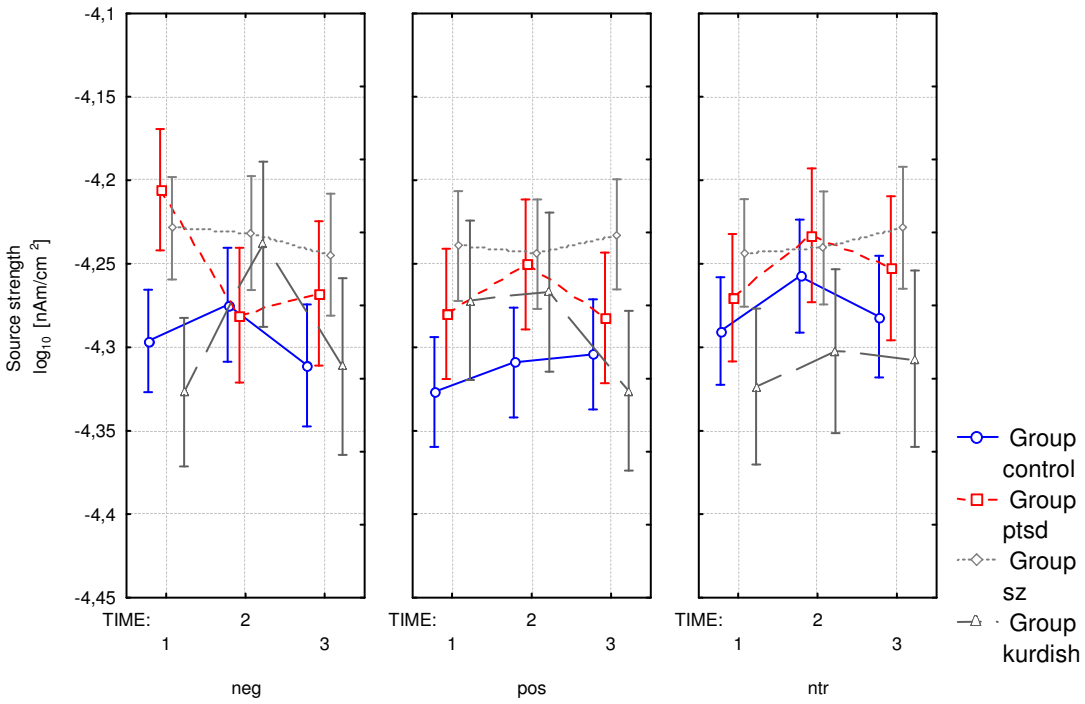
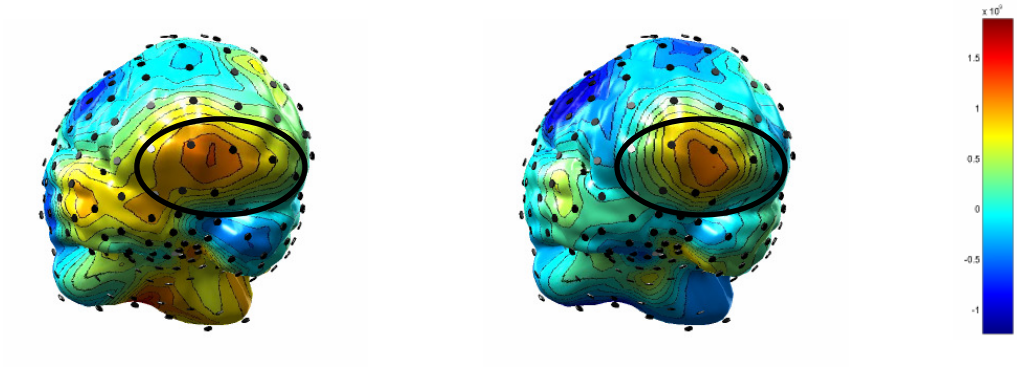


Figure 13: Category x Time x Group interaction. Displayed is the source strength in the time interval from 90-120ms in designated orbitofrontal areas. PTSD subjects show an extraordinarily high amplitude in response to the first presentation of negative pictures.

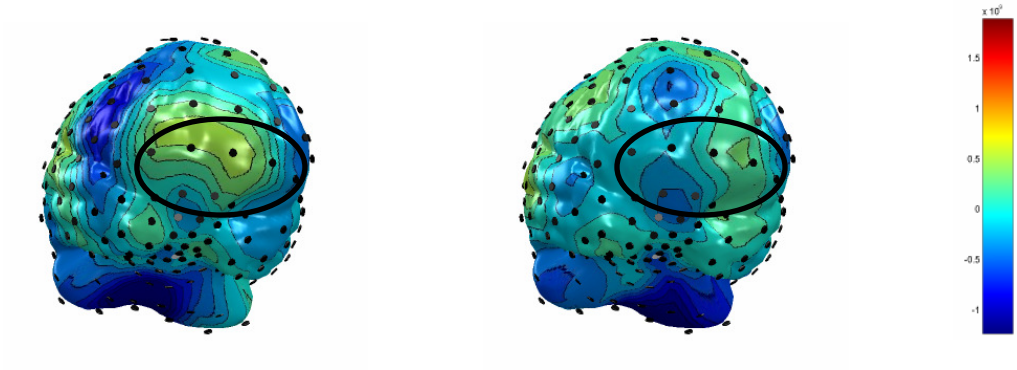
Therefore the overall ANOVA was gradually decomposed. Looking at the PTSD group, comparisons of the first presentation of the three picture categories ($F(2,28) = 3.73$; $p < .047$; $\varepsilon = .836$) and following post hoc tests confirmed the observations: negative pictures evoked a substantially higher amplitude than positive ($p < .019$) and neutral ($p < .038$) slides. The topographic difference mappings are displayed in Figures 14 a+b. This effect remained after exclusion of one extreme outlier ($F(2,26) = 3.67$; $p < .05$; $\varepsilon = .829$; post hoc: neg vs pos: $p < .02$; neg vs ntr: $p < .041$).

a.) negative - positive **b.) negative – neutral**

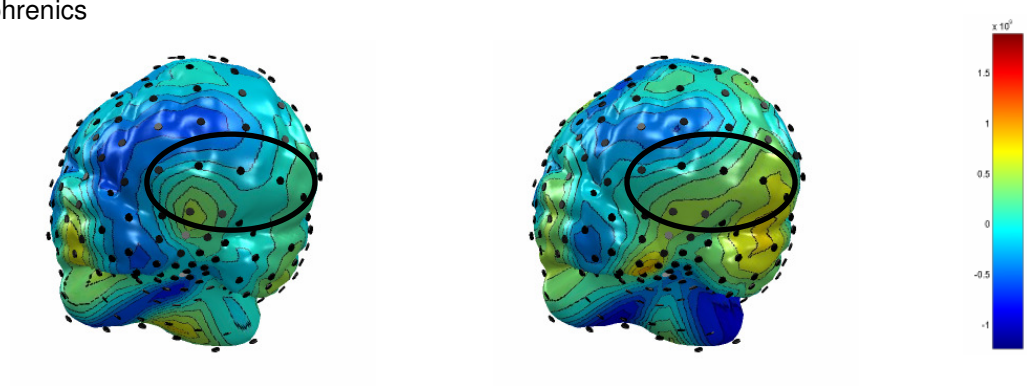
PTSD



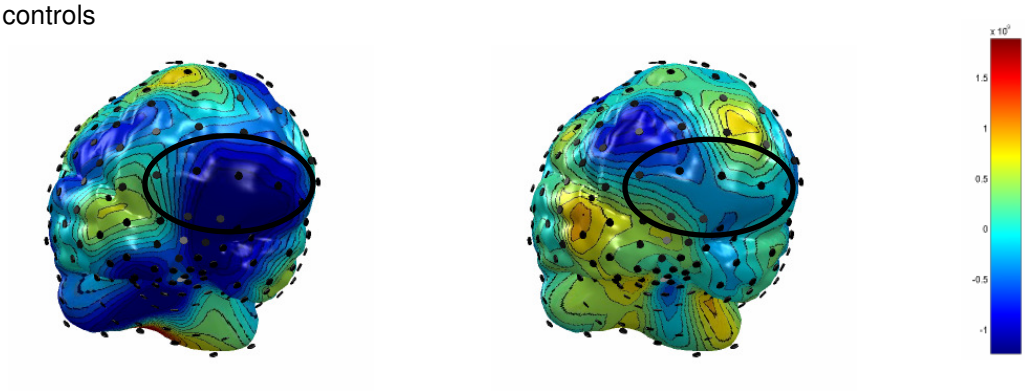
Controls



Schizophrenics



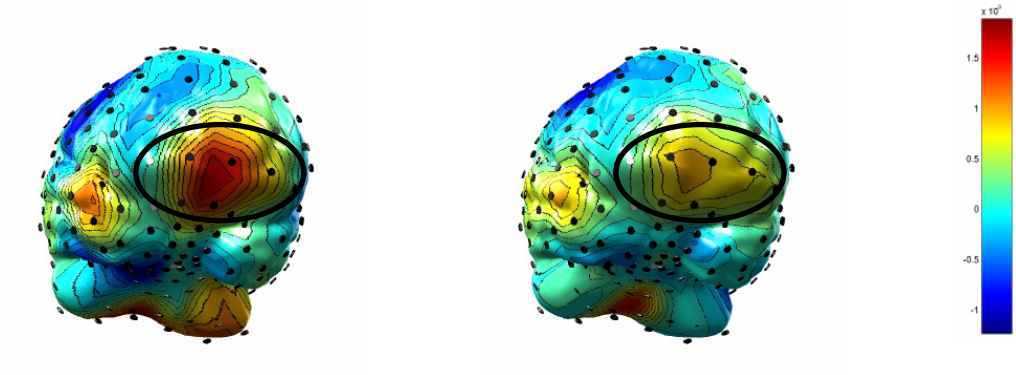
Kurdish controls



Figures 14 a+b: Topographic difference maps showing regions and strength of significant differences in the functional activity evoked by the first presentation of the three picture categories in the time interval from 90-120ms (Minimum Norm data, scale in nAm/cm^2). In contrast to all other groups the PTSD group shows significantly higher source strength for negative pictures. In Figure a the difference map of negative - positive pictures and in Figure b of negative - neutral pictures is shown.

As illustrated in Figure 13, a significant decrease in amplitude was recorded for the second and third presentation, as confirmed by ANOVA results ($F(2,28) = 3.6$; $p < .048$; $\varepsilon = .89$) and post hoc tests: 1st vs 2nd presentation: $p < .019$; 1st vs 3rd presentation: $p < .048$. Topographic difference maps are shown in Figures 15 a+b. After outlier exclusion a statistical trend remained ($F(2,26) = 2.8$; $p < .088$; $\varepsilon = .889$).

a.) 1st – 2nd **b.) 1st – 3rd**



Figures 15 a+b: Topographic difference maps of the functional activity evoked by the three presentations of negative pictures in the time interval from 90-120ms in the PTSD group (MN data, scale in nAm/cm^2). After an initial high amplitude, the following two presentations are characterized by habituation. Figure a shows differences between 1st - 2nd, Figure b between 1st - 3rd presentation.

The same analyses for the other three groups did not reveal any significant effects.

7.2.3 Inferior frontal regions (230-380ms)

A 4-way repeated measures ANOVA (within-subject factors Category, Time, Hemisphere; between-groups factor Group) was calculated. Schizophrenic patients showed a generally abnormal activity pattern compared to the other three groups. It was characterized by strongly augmented amplitudes for all conditions (significant Group main effect: $F(3,63) = 4.34$; $p < .009$). The Category x Time x Group interaction reached significance ($F(12,252) = 1.85$; $p < .049$; $\varepsilon = .911$) and can be seen in Figure 16.

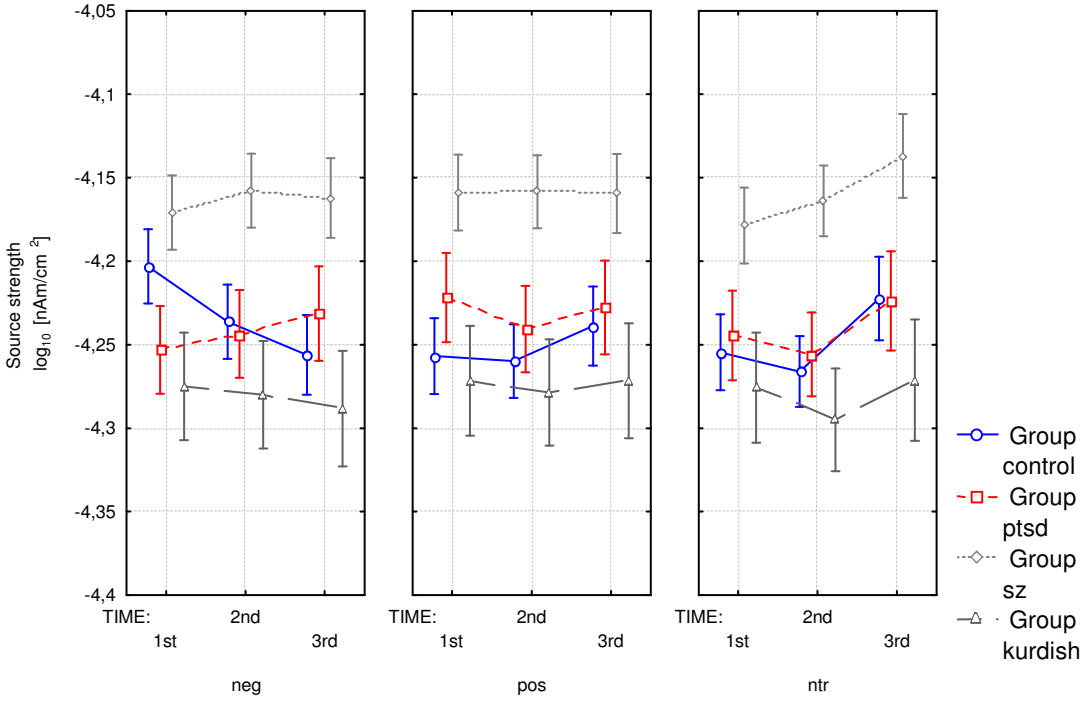


Figure 16: Category x Time x Group interaction. The source strength in the time interval from 230-380ms in designated inferior frontal areas is shown. Healthy controls showed a continuous suppression of the amplitude evoked by negative pictures from the 1st to the 3rd presentation. In contrast, the PTSD group was characterized by an increasing source strength.

Looking at Figure 16 it was hypothesized that the significant interaction was due to differential effects for the negative picture category. The responses to positive and neutral slides were similar across groups. Testing this hypothesis, 3-way repeated measures ANOVAs (within-subject factors Time, Hemisphere; between-groups factor

Group) were computed for each picture category separately. As expected a significant Time x Hemisphere x Group interaction was found only for negative stimuli ($F(6,126) = 2.32$; $p < .041$; $\varepsilon = .943$) (see Figure 17). This effect became even more significant after controlling for outliers (3 subjects in the healthy German control group, 2 subjects from the PTSD group and 1 subject from the Schizophrenic group) ($F(6,114) = 2.68$; $p < .021$; $\varepsilon = .943$).

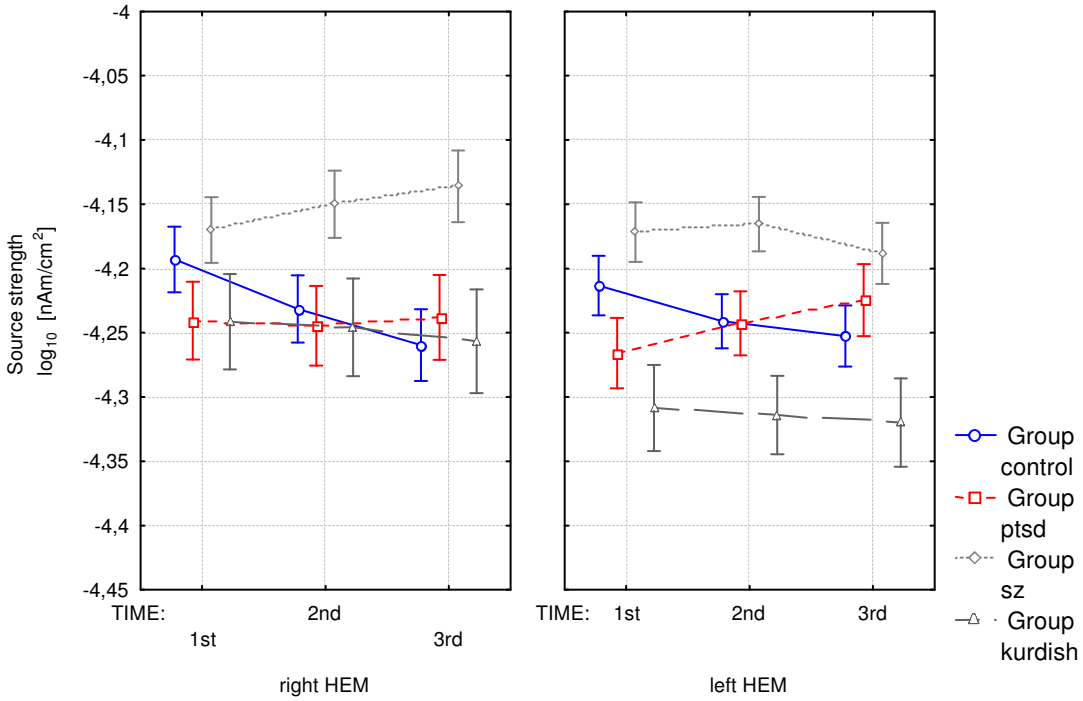


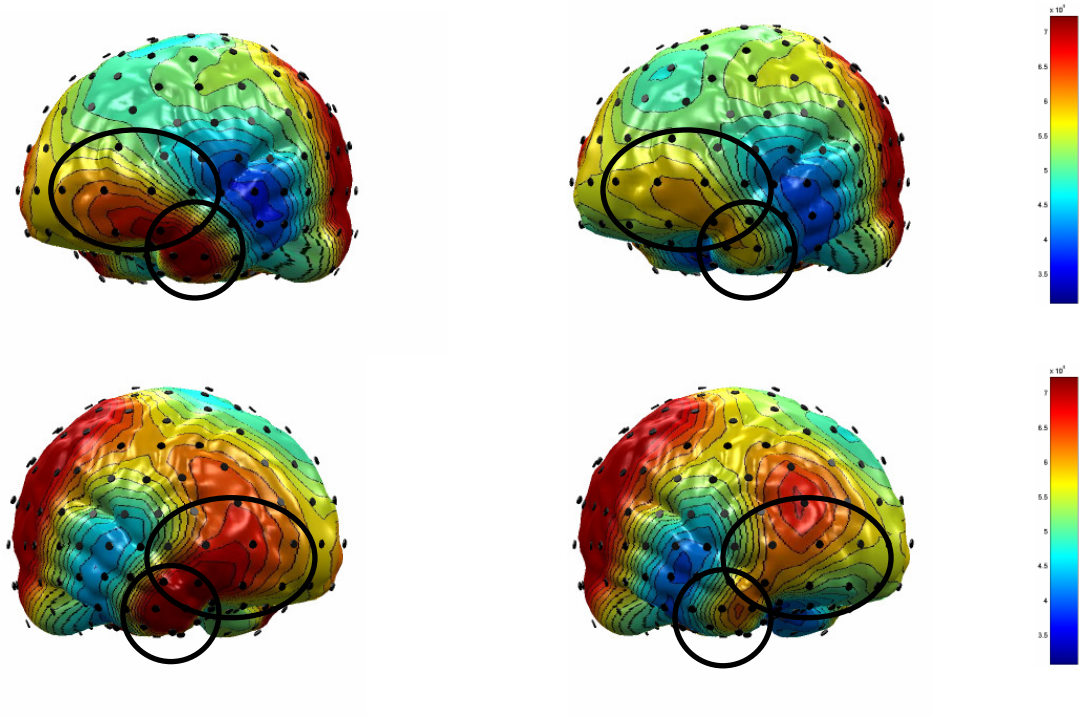
Figure 17: Time x Hemisphere x Group interaction for the negative picture category. Displayed is the source strength in the time interval from 230-380ms in designated inferior frontal areas. Healthy controls showed a significant suppression of the amplitude evoked by negative pictures from the 1st to the 3rd presentation in both hemispheres. The PTSD group was characterized by a significant increase in the left hemisphere. Schizophrenics had a significant increase in the right hemisphere.

Post hoc tests led to the following findings for negative pictures: a continuous significant suppression of the response from the 1st to the 3rd presentation was characteristic for the healthy German control group in both hemispheres (right hem: 1st vs 2nd: $p < .004$; 1st vs 3rd: p .001; 2nd vs 3rd: $p < .03$; left hem: 1st vs 2nd: $p < .032$; 1st vs 3rd: p .003; 2nd vs 3rd: n.s.). Contrary the inverse pattern was found for the PTSD group in the left hemisphere. A significant amplitude increase was evident (1st vs 2nd: n.s.; 1st vs 3rd: $p < .008$; 2nd vs 3rd: n.s.). Surprisingly a rise in amplitude was

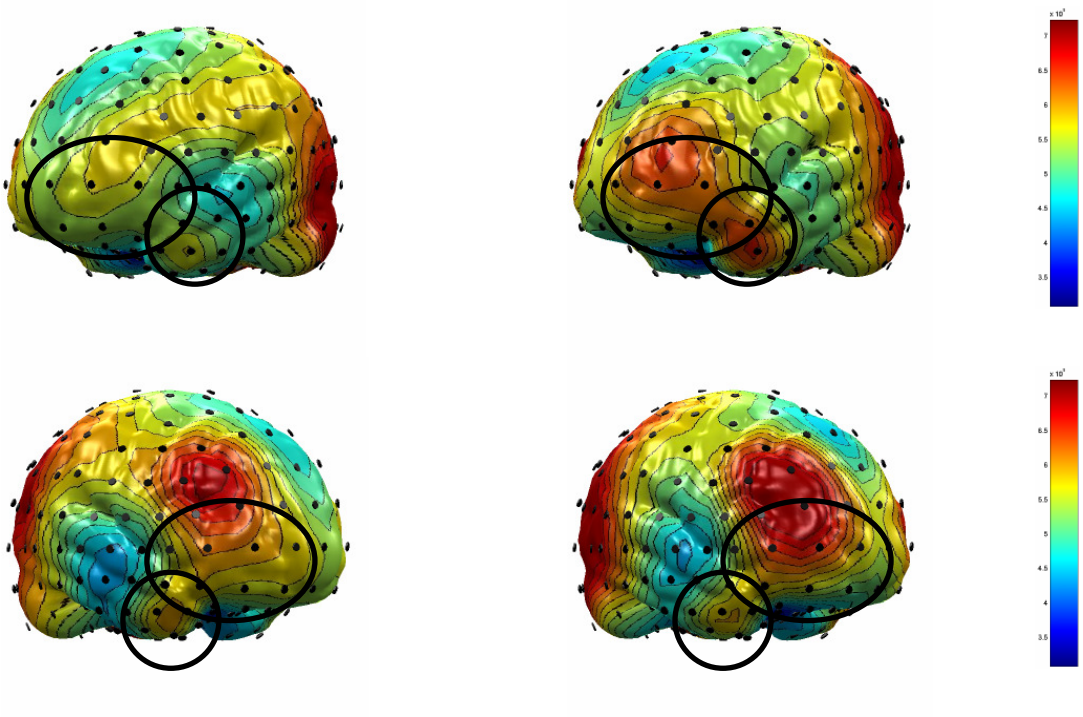
found for the Schizophrenic group, too, but in the right hemisphere (1st vs 2nd: n.s.; 1st vs 3rd: $p < .009$; 2nd vs 3rd: n.s.). Post hoc tests for the outlier controlled sample yielded very similar results and are therefore not further quoted. Figures 18 a-c present the Minimum Norm maps for these effects of differential functional activity.

1st presentation / neg **3rd presentation / neg**

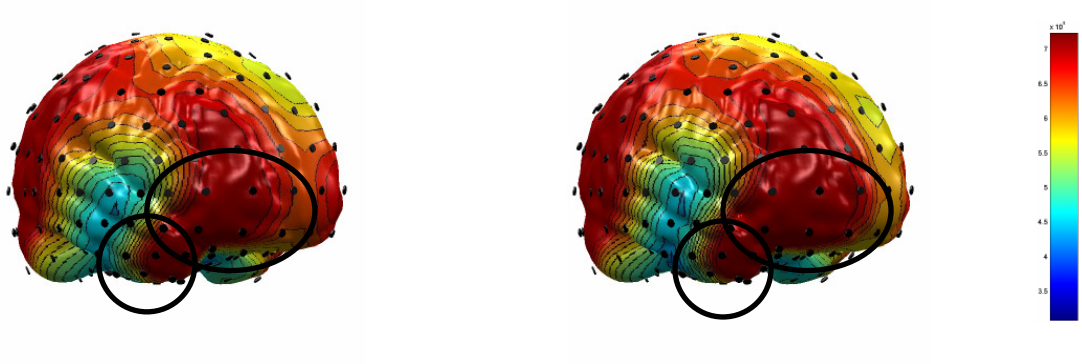
a.) Controls



b.) PTSD



c.) Schizophrenics



Figures 18 a-c: Minimum Norm maps of the functional activity evoked by the first and third presentation of negative pictures in the time interval from 230-380ms (MN data, scale in nAm/cm^2). Designated inferior frontal and anterior temporal areas are highlighted. Healthy German controls showed a bilateral activity suppression from the 1st to the 3rd presentation of negative slides. In contrast the PTSD group was characterized by a significant increase in the left hemisphere. The Schizophrenic group showed an increase in the right hemisphere.

Like in the overall ANOVA, the Schizophrenic group stands out by showing the highest overall source strength, demonstrated by a significant Group main effect ($F(3,63) = 3.87$; $p < .014$) and further post hoc tests.

7.2.4 Anterior temporal regions (230-380ms)

Like for the frontal regions a 4-way repeated measures ANOVA (within-subject factors Category, Time, Hemisphere; between-groups factor Group) was calculated for the anterior temporal lobes in the time interval from 230 to 380ms. A significant effect was found for the Category x Time x Group interaction ($F(12,252) = 1.95$; $p < .035$; $\varepsilon = 0.919$) (displayed in Figure 19).

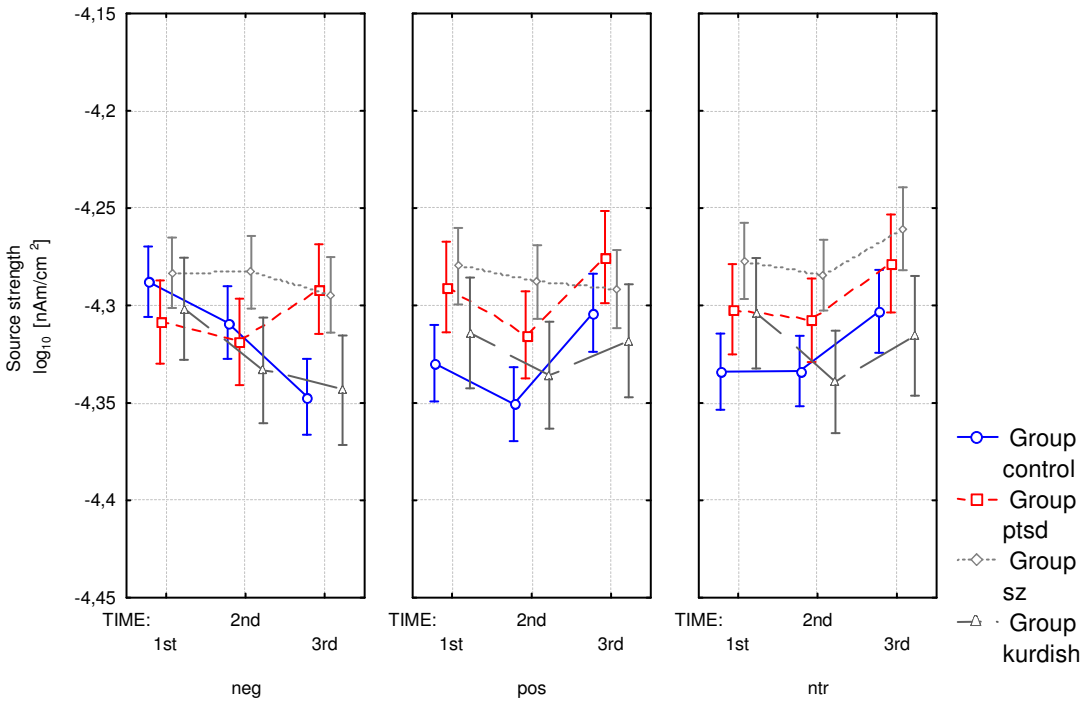


Figure 19: Category x Time x Group interaction. Displayed is the source strength in the time interval from 230-380ms in anterior temporal areas. ANOVA decomposition found significant group effects only for the negative picture category.

Calculating ANOVAs for each picture category separately, significant group effects were only found for the negative stimuli. Here the Time x Group interaction was highly significant ($F(6,126) = 3.36$; $p < .005$; $\varepsilon = 0.977$) (shown in Figure 20) and got even more significant after exclusion of outliers (2 German + 1 Kurdish control subjects, 3 PTSD subjects, 3 Schizophrenics) ($F(6,108) = 3.76$; $p < .003$; $\varepsilon = 0.946$).

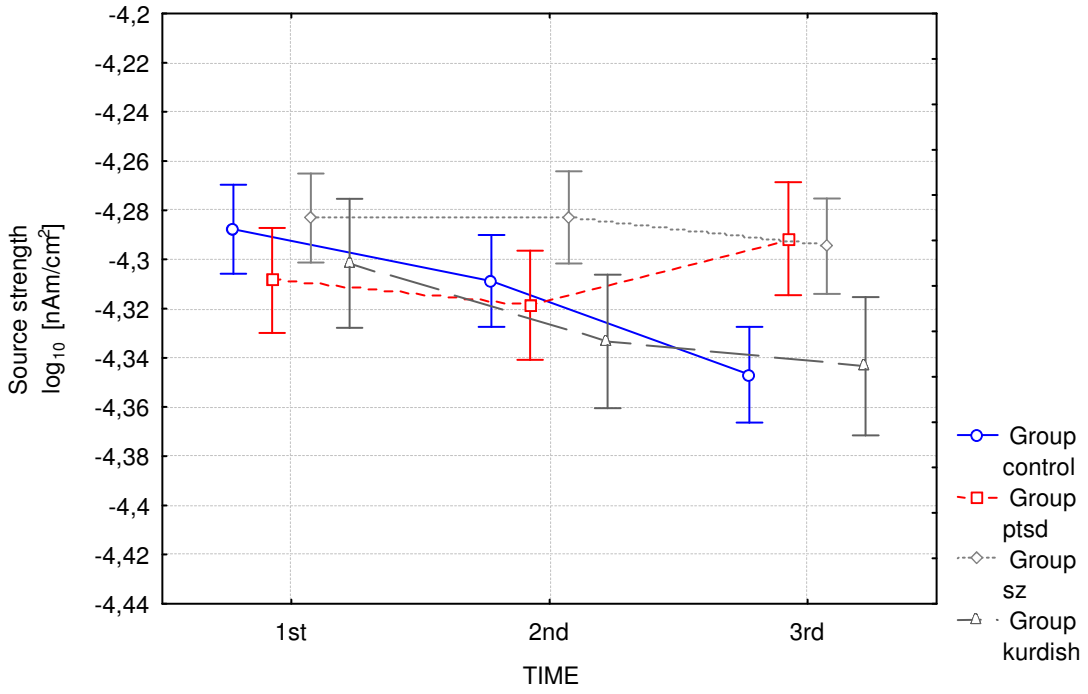


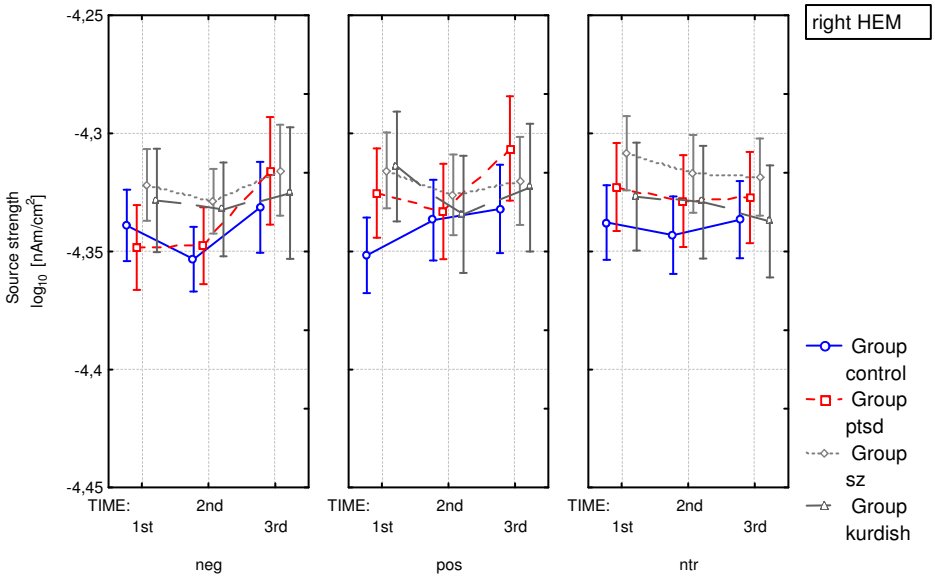
Figure 20: Time x Group interaction for the negative picture category. Displayed is the source strength in the time interval from 230-380ms in anterior temporal areas. German and Kurdish controls showed an amplitude suppression from the 1st to the 3rd presentation of negative pictures. Contrary a trend for an augmentation of the amplitude was found for the PTSD group.

Post hoc analyses for the outlier controlled sample revealed a significant response suppression for the group of healthy German controls from the first to the third presentation (1^{st} vs 2^{nd} : n.s.; 1^{st} vs 3^{rd} : $p < .004$; 2^{nd} vs 3^{rd}: $p < .033$). Similarly a trend for a suppressive effect was evident in the Kurdish control group (1^{st} vs 2^{nd} : n.s.; 1^{st} vs 3^{rd} : $p < .075$; 2^{nd} vs 3^{rd}: n.s.). The opposite pattern was seen in the PTSD group, where a statistical trend was found for an augmentation (1^{st} vs 2^{nd} : n.s.; 1^{st} vs 3^{rd} : n.s.; 2^{nd} vs 3^{rd}: $p < .088$). Topographic brain maps of the described effects can be seen in Figures 18 a-c (above).

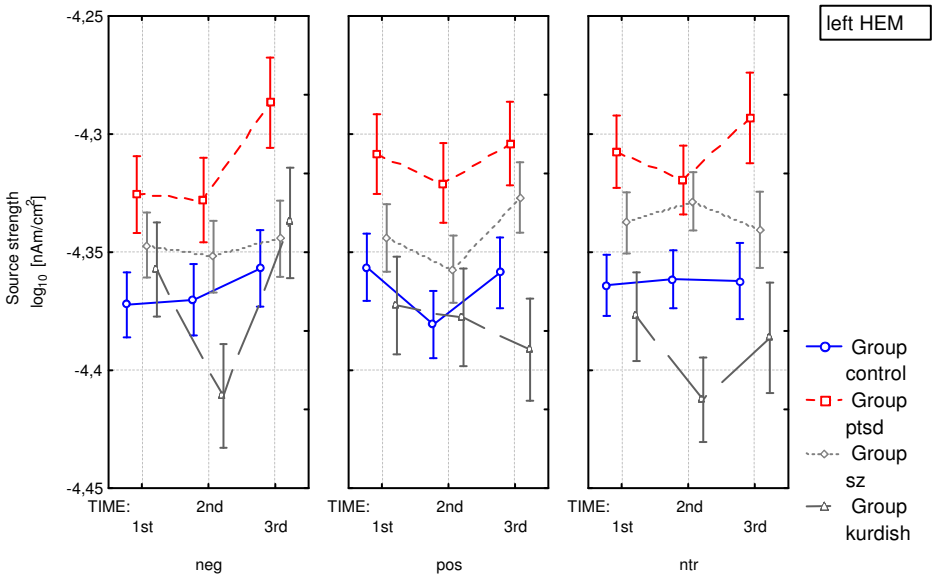
7.2.5 Temporal regions (380-600ms)

The 4-way repeated measures ANOVA (within-subject factors Category, Time, Hemisphere; between-groups factor Group) for designated temporal areas in the time interval from 380-600ms led to a significant Category x Time x Hemisphere x Group interaction ($F(12,252) = 2.2$; $p < .014$; $\varepsilon = .95$). Figures 21 a+b show this relationship.

a.)



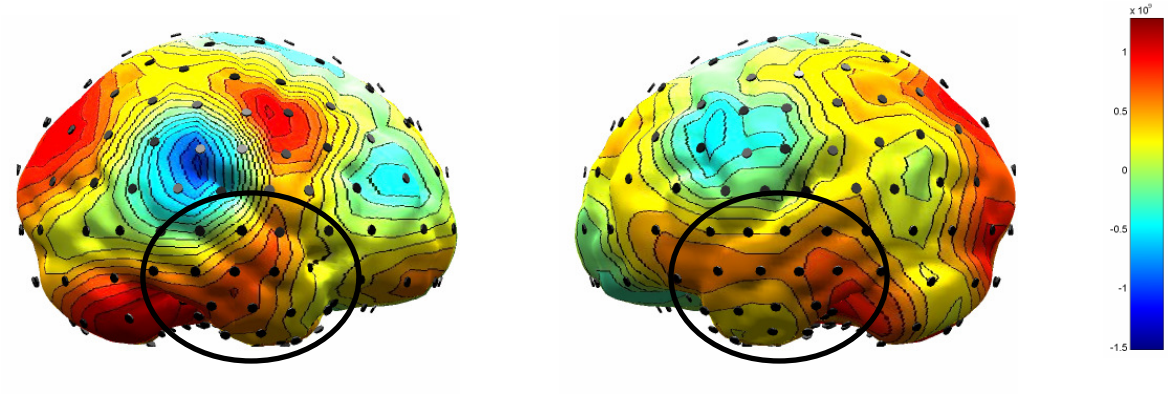
b.)



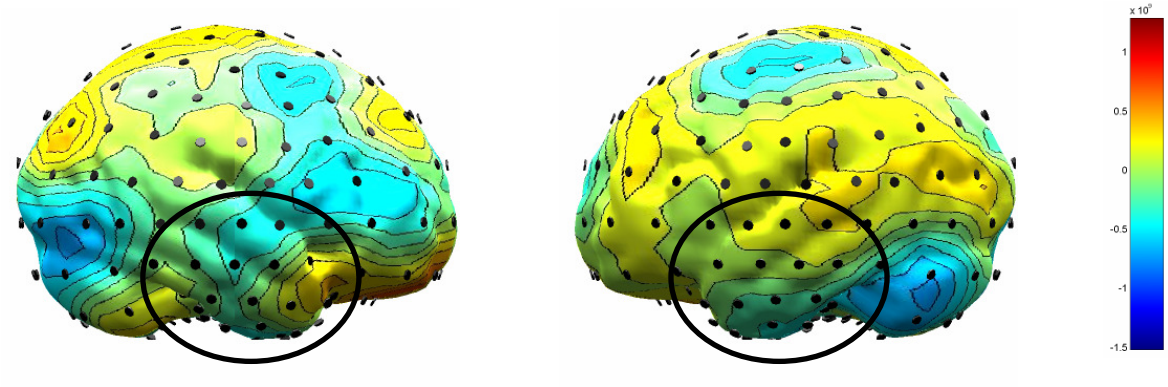
Figures 21 a+b: Category x Time x Hemisphere x Group interaction. Displayed is the source strength in the time interval from 380-600ms in designated temporal regions. Figure a shows results for the right, figure b for the left hemisphere.

Post hoc comparisons revealed the following results: the PTSD group showed a significant increase in amplitude for the negative pictures from the first to the third presentation in the right ($p < .006$) and left ($p < .001$) hemisphere (see also Figure 22 a). For positive and neutral stimuli respectively there were no significant differences between first and third presentation in either hemisphere. A different pattern of results was found for the healthy German control group: there was no significant difference between the first and third presentation of negative pictures in either hemisphere. Instead, in the right hemisphere a significant increase from the first to the third presentation was found for positive pictures ($p < .045$) (shown in Figure 22 b). Like for the PTSD group, no difference between first and third presentation was found for neutral pictures in either hemisphere. For the Schizophrenic and Kurdish control groups no differences comparing the first and third presentation of any of the picture categories were found. (ANOVA results after exclusion of outliers (3 healthy German controls, 1 PTSD subject): $F(12,236) = 1.95$; $p < .034$; $\varepsilon = .95$); similar results were obtained from post hoc tests and are therefore not further considered).

a.) PTSD group (negative pictures – 3rd - 1st)



b.) German controls (negative pictures – 3rd - 1st)



(positive pictures – 3rd - 1st)

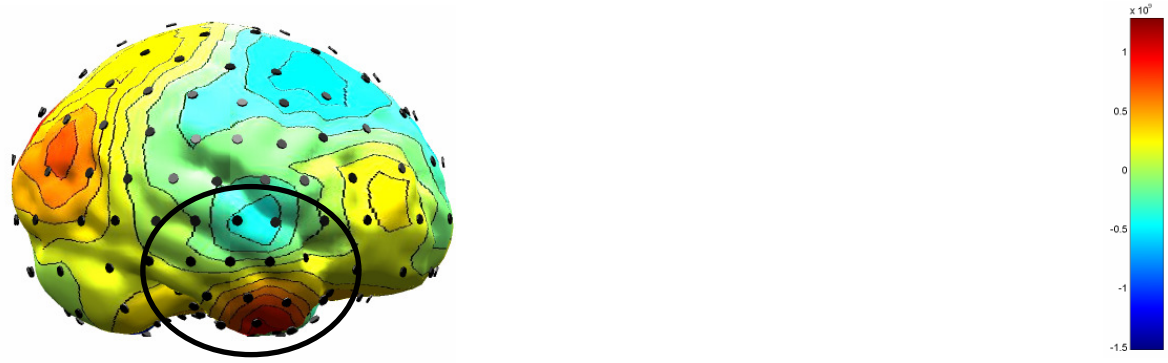


Figure 22: Topographic difference maps showing designated regions of the temporal lobe where a differential pattern of significant increases in the functional activity across presentations was found. The PTSD group is characterized by a bilateral increase in amplitude from the 1st to the 3rd presentation exclusively for negative pictures. The healthy German control group showed an exlcusive increase for positive pictures in the right hemisphere, but no increase for negative pictures in either hemisphere. This effect was significant in the time interval from 380-600ms (scale in nAm/cm^2).

7.3 Correlations between psychopathology and neuromagnetic data

The above findings from the neuromagnetic data analyses highlight the outstanding role of negative picture content in the PTSD group. A significantly higher source strength in response to negative pictures compared to the other two categories in orbitofrontal regions was found in the time interval from 90-120ms. Further, in the time range from 230-380ms the marked suppression of the amplitude in inferior frontal areas observed in the healthy German controls from the first to the third presentation of negative pictures was reversed in the PTSD group. Here no decrease was seen but rather an increase, although this might be due to a lack of initial response to the negative pictures. A similar result was found in anterior temporal regions in the same time interval. Furthermore, from 380-600ms left and right temporal regions responded with a significant activity enhancement in response to the third compared to the first presentation of negative pictures. To further evaluate the relationship between the exceptional reactions to negative picture content and PTSD psychopathology, correlations and later regression analyses were calculated.

a.) PTSD group

Product-moment correlations were calculated for selected neurophysiological parameters and symptomatic as well as demographic characteristics. In accordance to the effects found in the neuromagnetic data analyses, the following neurophysiological parameters were computed that entered the correlative analyses: for the time interval from 380-600ms the source strength in designated temporal regions at the first presentation of negative pictures was subtracted from the source strength at the third presentation to get an index of the magnitude of the amplitude rise. This was done for both hemispheres separately. Likewise difference indices for the amplitude changes between the first and third presentation of negative pictures respectively were calculated for the selected left inferior frontal and combined bilateral anterior temporal areas for the 230-380ms time interval. Further, the source strength of the first presentation of negative pictures in the time interval from 90-120ms in the selected orbitofrontal regions was used (values were logarithmized). Of the psychopathological / demographic characteristics the following parameters

entered the correlative analyses: from the PDS: the overall number of traumatic life events and the total symptom severity score, further the severity scores of single symptom clusters (reexperiencing, avoidance, arousal); the HAMD total score; years of formal education. The results can be seen in Table 7.

	1st presentation of neg. pic. (Source strength)	Difference index (3rd - 1st presentation of negative pictures) (Source strength)			
	orbitofrontal, 90-120ms	left inf. frontal, 230-380ms	ant. temporal, 230-380ms	temporal right HEM, 380-600ms	temporal left HEM, 380-600ms
Years of education	r = . 49 p = .066	r = .09 p = .761	r = -.11 p = .701	r = -.1 p = .733	r = -.28 p = .317
Number of events	r = .35 p = .204	r = .12 p = .662	r = .07 p = .792	r = .17 p = .547	r = .32 p = .244
Sev. of reexp. sym.	r = .37 p = .175	r = .23 p = .411	r = .44 p = .1	r = .3 p = .275	r = .59 p = .02
Sev. of avoid. sym.	r = .19 p = .488	r = .08 p = .773	r = .41 p = .133	r = .06 p = .841	r = .44 p = .103
Sev. of aro. symptoms	r = .67 p = .006	r = .45 p = .089	r = .45 p = .093	r = .5 p = .058	r = .54 p = .038
Tot. symtom severity	r = .51 p = .05	r = .32 p = .243	r = .54 p = .039	r = .36 p = .183	r = .66 p = .008
HAM-D total score	r = .26 p = .345	r = .22 p = .433	r = .34 p = .22	r = .0 p = .986	r = .42 p = .115

Table 7: Product-moment correlations between psychopathology / demographic characteristics and neuromagnetic activity for the PTSD group.

A significant positive correlation was found between the source strength in response to the first presentation of negative pictures in orbitofrontal areas (time interval 90-120ms) and the total PTSD symptom severity ($r = .51$; $p < .05$) (see also Figure 23). After exclusion of two outliers the results remained similar ($r = .58$; $p < .036$).

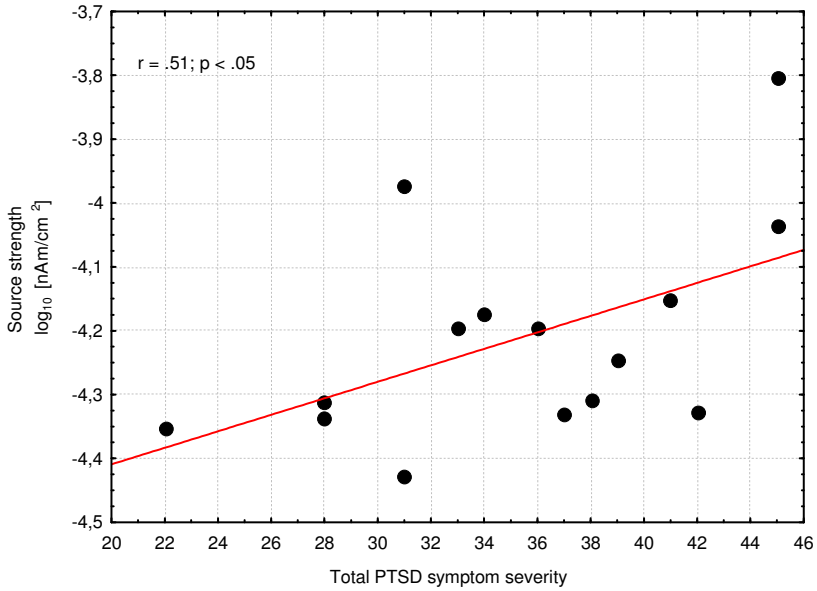


Figure 23: Positive correlation between overall PTSD symptom severity and source strength in response to the 1st presentation of negative pictures in orbitofrontal areas in the time interval from 90-120ms.

Specifically the severity of arousal symptoms seems to be responsible for this effect, since the correlation with the source strength reached a profound value of r = .67 (p < .006) (see also Figure 24).

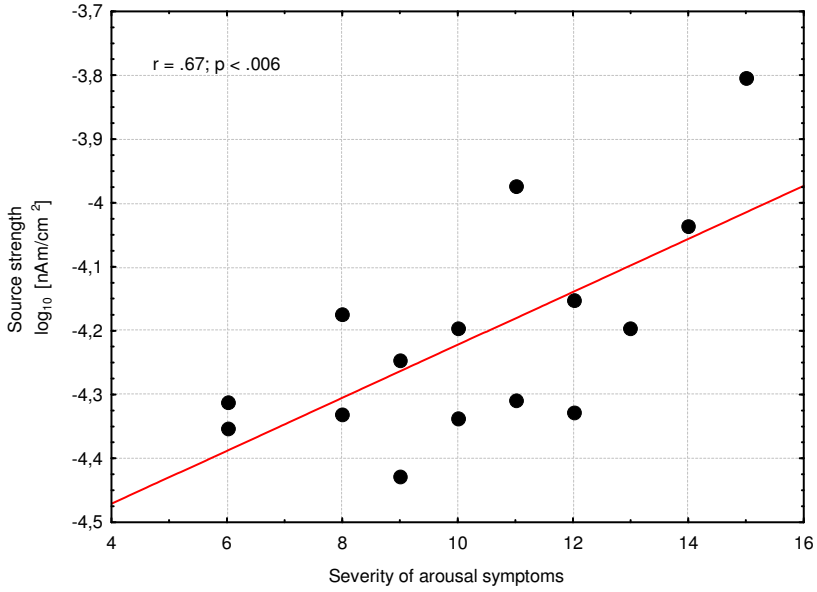


Figure 24: Positive correlation between severity of arousal symptoms and source strength in response to the 1st presentation of negative pictures in orbitofrontal areas in the time interval from 90-120ms.

To investigate the predictive value of each of the three symptom clusters of the PDS for the neuromagnetic responses in more detail, multiple regression analyses with the three subscales (severity of reexperiencing, avoidance, and arousal symptoms) as independent variables were computed. Although only a trend was found (R^2 = .32; p < .067) it became clear that the severity of arousal symptoms had the most prominent influence (β = .644). Reexperiencing and avoidance symptoms were not highly relevant (β = .162 and β = -.13). These findings are in line with the correlations.

For the activity enhancement in anterior temporal areas (time interval 230-380ms) a significant positive correlation was found with the overall PTSD symptom severity (r = .54, p < .039) (see also Figure 25). After outlier control (N = 2), results became even more significant (r = .62, p < .025). Multiple regression analyses with the three symptom clusters of the PDS did not reveal any significant effects (R^2 = .1; p < .261).

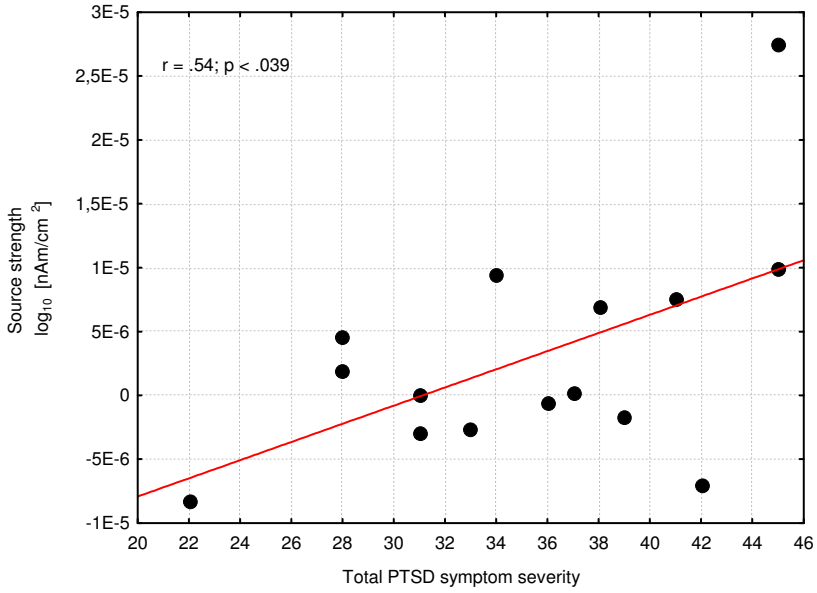


Figure 25: Positive correlation between overall PTSD symptom severity and and source strength increase from the 1st to the 3rd presentation of negative pictures in anterior temporal areas in the time interval from 230-380ms.

Further, the correlation of the total PTSD symptom severity with the degree of the amplitude rise in left temporal areas (time interval 380-600ms) reached a r-value of .66 ($p < .008$) (see also Figure 26) (after outlier control (N = 1): $r = .68$, $p < .007$).

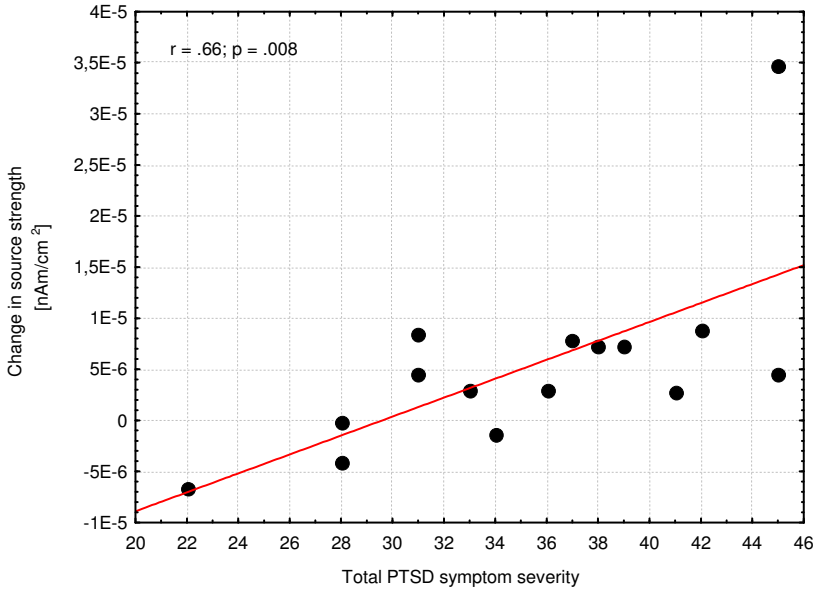


Figure 26: Positive correlation between overall PTSD symptom severity and source strength increase from the 1st to the 3rd presentation of negative pictures in left temporal areas in the time interval from 380-600ms.

Responsible for this effect are the high contributions of the severity of reexperiencing ($r = .59$, $p < .02$) (shown in Figure 27) and arousal ($r = .54$, $p < 038$) (shown in Figure 28) symptoms. After outlier control (N = 1) only severity of reexperiencing symptoms had a significant correlation with the change in source strength (reexperiencing: $r = .58$, $p < .029$; arousal: $r = .45$, $p < .105$).

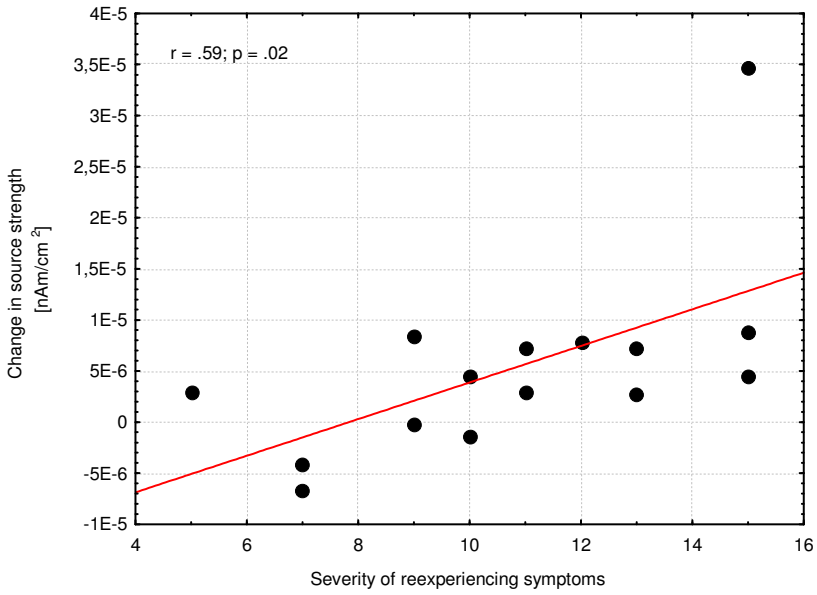


Figure 27: Positive correlation between severity of reexperiencing symptoms and source strength increase from the 1st to the 3rd presentation of negative pictures in left temporal areas in the time interval from 380-600ms.

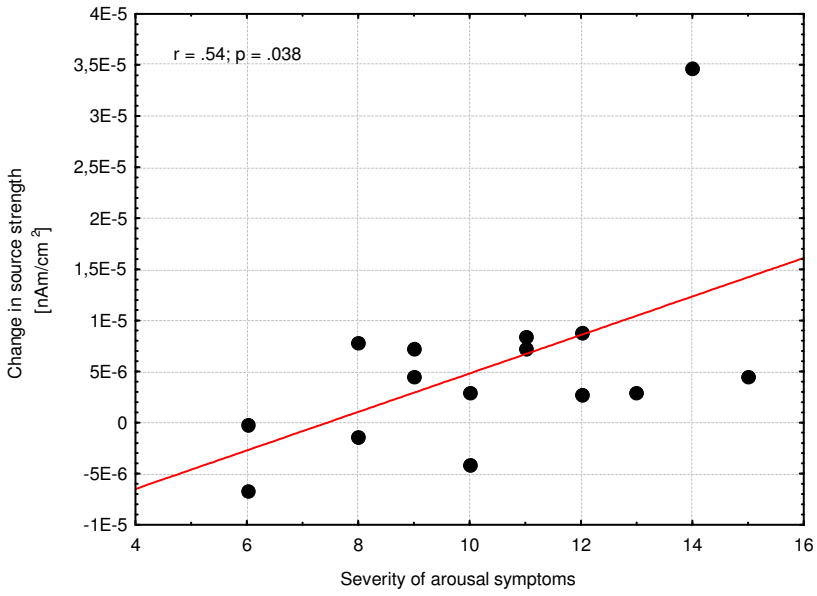


Figure 28: Correlation between severity of arousal symptoms and source strength increase from the 1st to the 3rd presentation of negative pictures (left temporal areas, time interval from 380-600ms). After outlier control the correlation did not reach significance anymore.

Multiple regression analyses including the three PDS symptom clusters were performed to evaluate their respective relative predictive importance. A statistical trend was found (R^2 = .3; p < .076). Analyses revealed that reexperiencing symptoms (β = .395) had the biggest influence, followed by arousal (β = .336) symptoms and that avoidance (β = .083) played no big role.

b.) Schizophrenic patients

Like for the PTSD group analyses were done for the group of Schizophrenic patients to investigate whether psychopathological dimensions were related to the same neuromagnetic parameters. No significant correlations, nor multiple regression analyses were found when the following psychopathological / demographic measures entered the analyses: years of formal education, amount of medication (chlorpromazinequivalent), PANSS-P, PANSS-N and PANSS-G scores.

c.) Healthy German controls

To investigate if the same neuromagnetic parameters that were predictable by or correlated with certain symptoms of fear in the PTSD group had a similar relationship with different degrees of non-pathological state or trait anxiety in the healthy German control group, product-moment correlations and multiple regression analyses were calculated. For control reasons the level of education and BDI scores (all not clinically relevant) were also included. Table 8 shows the results of the correlative analyses.

	1st presentation of negative pictures (Source strength)	Difference index (3rd – 1st presentation of negative pictures) (Source strength)			
	orbitofrontal, 90-120ms	left inf. frontal, 230-380ms	ant. temporal, 230-380ms	temporal right HEM, 380-600ms	temporal left HEM, 380-600ms
Years of education	r = .13 p = .570	r = -.06 p = .782	r = -.19 p = .414	r = .44 p = .047	r = .06 p = .796
BDI total score	r = .39 p = .083	r = .01 p = .973	r = -.26 p = .253	r = .48 p = .028	r = -.05 p = .816
STAI-state score	r = .53 p = .014	r = -.15 p = .506	r = -.11 p = .638	r = -.31 p = .166	r = -.41 p = .062
STAI-trait score	r = .28 p = .222	r = -.28 p = .223	r = -.43 p = .052	r = .18 p = .432	r = -.24 p = .287

Table 8: Product-moment correlations between non-pathological degrees of state and trait axiety, BDI score, level of education, and neuromagnetic activity for the healthy German control subjects.

A significant positive correlation was found between source strength in response to the first presentation of negative pictures in orbitofrontal areas (time interval 90-120ms) and the STAI-state score (r = .53; p < .014) (shown in Figure 29).

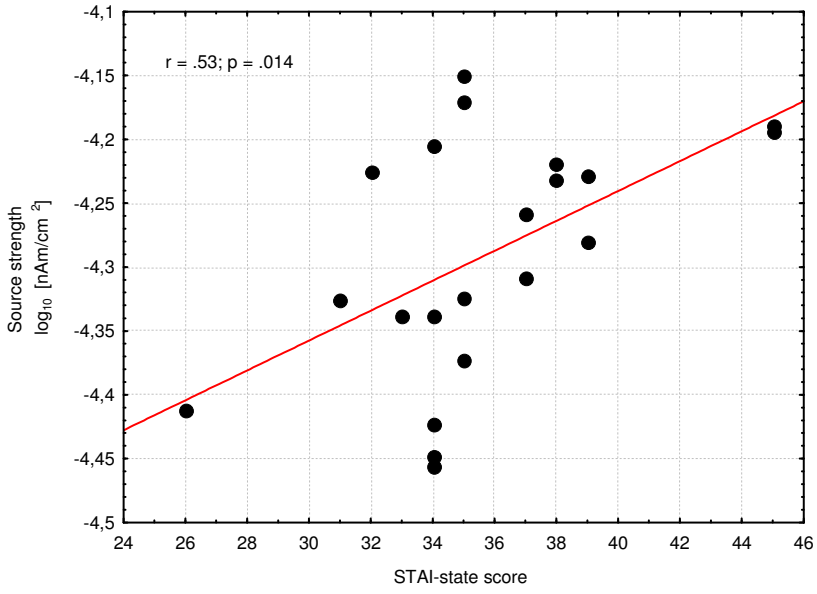


Figure 29: Positive correlation between non-clinical STAI-state scores and source strength in response to the 1st presentation of negative pictures in orbitofrontal areas in the time interval from 90-120ms.

Further, the BDI score was positively correlated with the amplitude increase in response to negative pictures in right temporal areas (time range 380-600ms) (r = .48; p < .028) (see Figure 30).

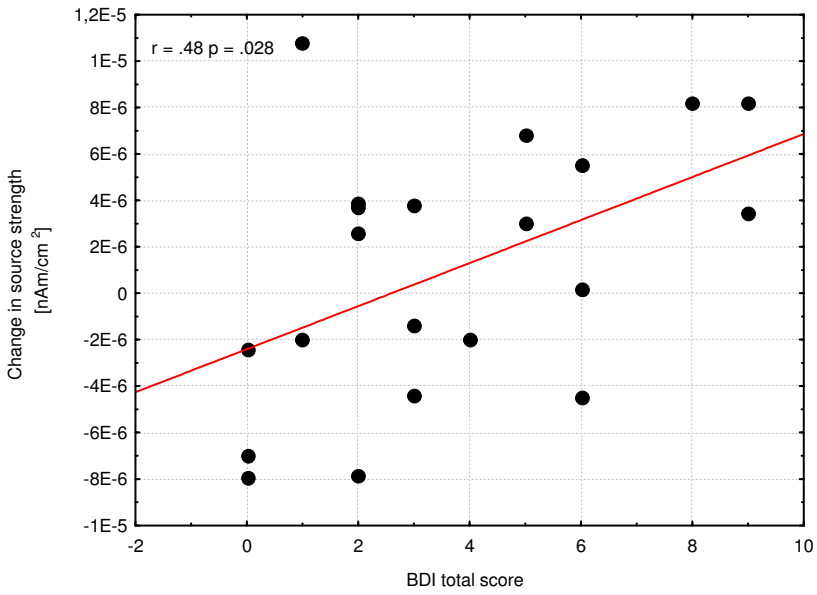


Figure 30: Correlation between non-clinical BDI scores and source strength increase from the 1st to the 3rd presentation of negative pictures in right temporal areas in the time interval from 380-600ms.

Similarly, a correlation was found with the level of education (r = .44; p < .047) (see Figure 31).

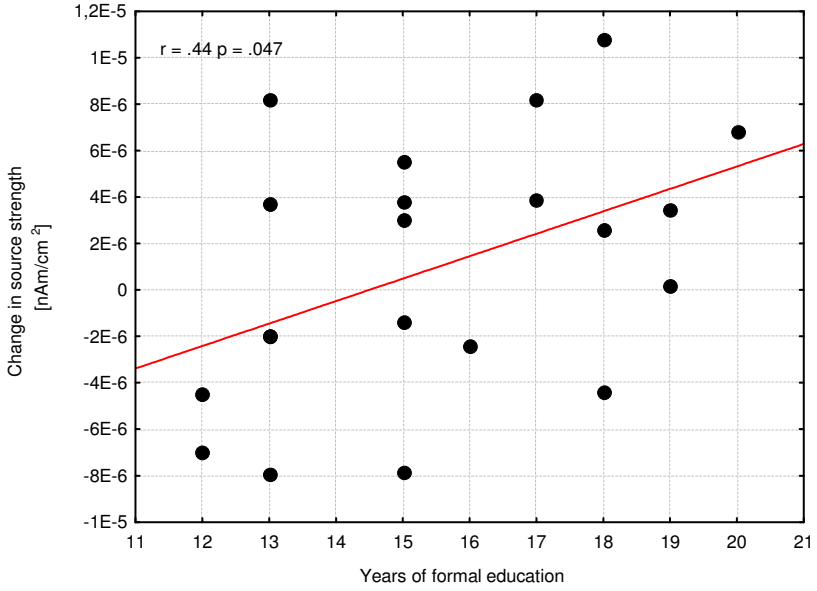


Figure 31: Correlation between education and source strength increase from the 1st to the 3rd presentation of negative pictures in right temporal areas in the time interval from 380-600ms.

When all demographic variables entered a multiple regression analysis, state anxiety was one relevant predictor for the source strength in response to negative pictures in orbitofrontal areas in the time interval from 90-120ms (R^2 = .31; $p < .041$; β = .625). Further, the predictive value of the BDI scores for the amplitude increase in response to negative pictures in right temporal areas in the time range from 380-600ms was confirmed (R^2 = .34; $p < .028$; β = .543).

d.) Kurdish controls

Although the severity of depressive symptoms in the Kurdish control group was below clinical relevance in all subjects, it was analyzed if varying degrees of non-pathological depressive symptoms were associated with the identical neuromagnetic parameters used for the other groups. Further, none of these subjects had a PTSD symtomatology, but all of them except for one had at least experienced one potentially traumatic event. Therefore it was investigated if the total number of such events was associated with certain characteristics of the named neuromagnetic parameters. The level of education was also included in the analyses. Neither the correlative, nor the multiple regression analyses revealed any significant results.

8 Discussion

The present study was aimed at elucidating three characteristics of abnormal emotional processing in PTSD. First, evidence was sought for a hypersensitive alarm system that would be rapidly activated in the presence of threatening stimuli. It was particularly focussed on the exact temporal onset of this system in the presence of fear-related material. Second, a distorted mnemonic filter in form of a decreased or even lack of repetition suppression was hypothesized and investigated. Third, proof was sought for a selective recognition memory bias for aversive stimuli. The latter was hypothesized on the assumption of selective sensitivity of brain networks involved in the retrieval of aversive trauma-related information from the “hot” memory system. New aversive stimuli were supposed to become easily integrated into this fear network by association. The activation of an emotional and strongly sensory-perceptual fear-memory network was sought to be correlated with an activity increase in the temporal cortex. These three suggested pathologic features of emotional processing are sought to be PTSD-specific and are supposed to contribute to the maintenance of the disorder.

8.1 Summary of the main results

First, PTSD patients were the only group showing a differential orbitofrontal brain response to the first exposure of the three picture categories. The OFC of these patients showed an extraordinarily high amplitude in response to fear-related material in a time interval from 90-120ms. The source strength was positively correlated with the severity of arousal symptoms. Multiple regression analyses confirmed the predictive value of arousal symptoms for the orbitofrontal response. In further confirmation of the relationship between arousal and early orbitofrontal activity is the finding of of a positive correlation of orbitofrontal source strength with non-clinical STAI-state scores from the healthy German controls.

Second, whereas healthy controls showed strong repetition suppression in inferior frontal and anterior temporal areas across repetitions of negative pictures (time interval 230-380ms), PTSD patients rather showed an activity increase. However, the effect in the PTSD group might be due to a decreased initial response

to the aversive slides. The observed activity increase in anterior temporal areas in the PTSD group was positively correlated with the overall PTSD symptom severity.

Third, PTSD patients were characterized by a significant amplitude increase in temporal areas from the first to the third presentation of aversive pictures. This effect was found between 380 and 600ms. The increase was positively correlated with overall PTSD symptom severity. Multiple regression analyses revealed that mainly severity of reexperiencing symptoms contributes to this effect. Behavioral results are in line with these findings by showing that recognition performance was best for fear-related pictures. Impairments were found for positive and neutral slides. Contrary, healthy German controls showed a significant temporal amplitude increase for positive pictures. Although controls' recognition performance did not differ significantly between the three picture categories, d' was highest for positive slides.

8.2 A hypersensitive brainstem-amygdala-cortical alarm system

8.2.1 Initial emotional modulation of OFC activity relies on unconscious subcortical appraisal

Focussing on the PTSD group, the first presentation of negative pictures evoked the strongest activation in the OFC. The amplitude in response to aversive slides was significantly higher compared to positive and neutral pictures that did not differ from each other. This effect was observed in an early time interval from 90-120ms. It was further seen that the two repetitions of the negative pictures were associated with a significantly weaker source strength that was comparable to the source strengths in response to positive and neutral stimuli. This amplitude decrease indicates adaptation to the aversive pictures or more likely a shift from an unconscious processing route to a processing modus that relies more on familiarity information. This shift is assumed to be accompanied by suppression of access to unconscious information and will be described later. Neither the two healthy, nor the clinical control group showed a differential orbitofrontal brain response to the three picture categories. No differences in early OFC activation between the different picture categories were found for any of the control groups.

These findings support the results from the study by Junghoefer et al. (2003). The authors found an early emotional modulation of OFC activity that was limited to the PTSD group. In the time interval from 60-110ms, PTSD patients were characterized by a significantly higher orbitofrontal amplitude when they were shown negative as compared to neutral pictures. However, the effect was weaker in the present study. Although the effect of differential affective modulation of OFC was significant within the PTSD group, the between groups comparison was not significant, as was the case in the Junghoefer study. One major difference between the two studies is the duration of stimulus presentation and of the interstimulus interval (ISI). Whereas Junghoefer applied the Rapid Serial Visual Presentation (RSVP) paradigm, where each picture was presented for only 333ms and without an ISI, stimulus duration in the present study was 1200ms with a fixed ISI of 600ms. RSVP can be characterized as a paradigm where stimulus processing might be restricted due to its short presentation and the rapid succession of stimuli (e.g. Potter, 1976). According to Raymond et al. (1992) the rapid succession of stimuli in RSVP paradigms causes an interference with visual processing. While identification of the first stimulus is still underway, attention cannot be consistently reallocated to the next stimulus presented during a critical interval of 450ms. Thereby visual processing of the succeeding stimulus is limited. When conscious cortical visual perception is restricted, unconscious subcortical processes may be amplified. The RSVP paradigm used by Junghoefer et al. represents a paradigm where stimulus perception lies between an unconscious, subliminal and a fully conscious, complete visual analysis. Visual perception is thereby restricted in that study. As a consequence, stimulus processing relies more on subcortical, amygdala based mechanisms. The more conscious attentional resources are available for a given stimulus, the stronger the interference with subcortical processes. This interferences were demonstrated in several studies.

Morris et al. (1999) for example demonstrated that conscious and unconscious visual perception are associated with activation of slightly different brain areas. The employed backward masking procedure is likely to disrupt certain cortical processes while leaving the subcortical tectothalamo-amydgala pathway intact. The processes accomplished by the subcortical pathway may be amplified by unconscious perception. Masking stimuli have been shown to inhibit responses in V1 in animal studies (Macknik et al., 1998). The other way round, when subjects consciously

perceive a visual stimulus, access to unconsciously processed information is affected (Jolij et al., 2005). In that study affective blindsight was induced in healthy volunteers by transcranial magnetic stimulation (TMS) of the occipital cortex. Subjects had to indicate as quickly as possible the emotional expression of a deviant facial stimulus within a set of four facial expressions, three of them being identical. Furthermore, the location of the deviant stimulus had to be determined. TMS was applied at critical delays after stimulus onset. It was shown that localization was not possible for the subjects but that affective discrimination was significantly above chance level. When stimulus visibility / familiarity increased across the experiment due to training, affective blindsight performance did not improve. Rather a performance decrease in the discrimination of the different emotions was observed. This means that increased stimulus visibility suppressed the affective blindsight effect. The authors concluded that access to unconscious information is only possible when stimulus visibility is below a certain threshold, so that the subject is insecure about the stimulus content. When a subject consciously perceives a stimulus, access to unconscious information that is processed in the amygdala is repressed. On the other hand, when conscious information is not available, the system relies more strongly on unconscious information for response generation. This means that subjects are “blindly led by emotions”, but only in the case when explicit, conscious information is not available.

Several other studies also found that masked aversive pictures elicit stronger behavioral reactions and greater amygdala activation than the same stimuli when unmasked (Kubota, 2000; Mogg, 1999). When more processing time or attentional resources are available for a single aversive stimulus, early unconscious subcortical evaluations might be modified or suppressed (Murphy et al., 1993).

These findings are relevant for the comparison of the present study with the Junghoefer study: the RSVP in the Junghoefer study results in a stimulus analysis that might amplify the subcortical perceptual processes. Therefore the effects of emotional modulation of early aversive picture processing seen in PTSD patients might be stronger in that study. The design of the present study provides subjects with more attentional resources for a given stimulus, thus the modification or suppression of subcortical (amygdala based) evaluation is more likely. In accordance with the findings from Jolij, it is suggested that the unconscious information about the negative valence of the employed stimuli is repressed to a stronger degree in the present paradigm than with RVSP. Nevertheless repression is not complete and

PTSD subjects showed a significantly higher subcortically mediated OFC activation to aversive as compared to positive and neutral pictures. The same mechanism of partly repressed access to unconscious information in case of stimulus familiarity can also explain why the two repetitions of negative slides were associated with a significant amplitude decrease. Increased visibility or familiarity due to earlier exposure to the stimulus might affect the unconscious information. The conscious knowledge of the stimulus content that subjects had at the time of the two repetitions may affect unconscious information.

The demonstration of early emotional modulation of OFC activity in the PTSD group in the present study, although weaker than in the Junghoefer study, is an extension of the effect to a design with greater visibility of the stimulus. For a more pronounced emotional modulation of OFC activity, a masked or subliminal stimulus presentation without ISIs seems more suitable.

8.2.2 Arousal mediates early orbitofrontal activity in response to self-related fearful material

The initial encounter with the aversive pictures triggered an extraordinarily strong activation of OFC in the PTSD patients. This effect is most likely mediated by emotional arousal and the noradrenegic (NE) / locus coeruleus (LC) system that inervates amygdala and OFC. This hypothesis is supported by the finding that the severity of PTSD arousal symptoms was positively correlated with the source strength in response to the first presentation of negative pictures. This was further confirmed by the multiple regression analysis that produced the highest β-weight for arousal when all PTSD symptom clusters were considered. Additional support for the mediating role of emotional arousal on amygdala and OFC activity comes from the finding that in healthy subjects the STAI-state score was also positively correlated with the magnetic source strength in response to negative pictures. The items from the STAI-state questionnaire are related to the acute stress level of the subject. This incorporates to the biggest extent the subjective arousal level. Typical items deal with excitement, calmness, agitation, anxiety, or acute distress.

It can be argued that the positive pictures employed in the present study should also produce a pronounced OFC activity when arousal is the crucial factor.

Although the positive pictures were rated as slightly less arousing than the negative ones (M = 4.9 vs M = 5.9) on the SAM, this difference might not be sufficient to explain the relative lack of OFC activation. Phan et al. (2004) observed that the degree of emotional self-relatedness was associated with the activity of ventromedial prefrontal cortex. In a trial-related fMRI study subjects watched various pleasant, unpleasant, and neutral pictures from the IAPS. In addition, subjects were required to make a self-related judgement via button press of the extent to which they had a personal association with each picture. This self-referential evaluation means that subjects considered whether the stimulus has any personal relevance or salience based on personal life experience. For example the picture of a barking dog might have some negative personal emotional salience because the subject was bite by a dog when he/she was a child. fMRI results indicated the ventromedial prefrontal cortex to be essential for this type of appraisal. The more self-related a picture content was, the more activation was evoked in this brain region. Generally, these results suggest that the ventromedial prefrontal cortex is crucial for the interpretation of incoming stimuli with regard to personal history. Further support for this role comes from imaging studies that show activation of the same region when personal affect-laden life events are recalled (George, 1996; Reimann, 1997). For the present findings it can be argued that the negative pictures had strong self-related emotional salience for the PTSD patients due to their traumatic life experiences. The personal relevance of the positive arousing stimuli is less strong. Therefore the slides with aversive content evoked the strongest OFC activation in the PTSD group.

8.2.3 NE and CRF as contributors to a hypersensitive alarm system in PTSD

The detection of a threatening stimulus via the subcortical secondary visual pathway, as outlined in the introduction, activates noradrenergic neurons in the LC. NE is secreted and increased in the amygdala and OFC. Amygdala and OFC form a functional unity. The amygdala initially determines the reinforcing/punishing value of a given stimulus. The more salient a stimulus, the stronger the neural activation (Breiter, 1996). Many authors underline the specialization of the amygdala for processing fear-relevant or threatening stimuli (Adolphs, 1994). However, it might be that threatening stimuli are just more salient than high arousing positive stimuli,

because the former are more vital for survival. The OFC receives a copy of the stimulus representation with its emotional connotation to initiate an adaptive behavior. Similar to the amygdala, the OFC shows stronger activation in response to more intense stimuli (Blair, 1999).

The fact that only PTSD subjects showed the particularly high OFC amplitude in response to negative pictures suggests that the amygdala-OFC unit is sharpened or hypersensitive in this population. The underlying mechanism might be the chronically exaggerated activity of noradrenergic projection neurons in the LC that project to amygdala and OFC. Furthermore, long-term plastic changes induced by chronically elevated CRF might further contribute to the hypersensitivity. Chronic and uncontrollable stress has been demonstrated to increase the responsivity of neurons in the LC when an excitatory stimulus is encountered (Simson, 1994). NE leads to an enhanced neuronal excitability (McCormick, 1991) and also activates the HPA-axis. Activation of the HPA-axis includes the secretion of CRF that further increases the excitability of the amygdala (Rainnie, 1992; 2004). Both, CRF and NE have been shown to be chronically elevated in PTSD (Bremner, 1997; Geracioti, 2001). Bremner used a specific radioimmunoassay to measure CRF and found higher levels in PTSD patients as compared to controls. Evidence for NE hyperactivity in PTSD comes from a bunch of peripheral studies. Sympathetic functioning is increased, as can be observed in heart rate responses, blood pressure, and skin conductance (Blanchard, 1996). Disturbed sleep functions, characterized by decreased total sleep, an increased number of awakenings, and increased rapid eye movement activity, are also common in PTSD patients (Mellman, 1995; Ross, 1999). These distortions can be regarded as central nervous system alerting. Furthermore, exaggerated startle reflexes have been found (Orr, 2002), as well as elevated plasma levels of adrenaline and NE in response to stress (Blanchard, 1991). NE plays a crucial role in arousal processes. Enhanced activity of the LC results in high levels of alertness. It has been shown that acute and chronic stress lead to elevated NE concentrations in the amygdala, prefrontal cortex, and other brain areas (Bremner, 1996; Tanaka, 2000).

It was assumed from PTSD patients' subjective reports after the present experiment that the stress level in the present study was moderate. At moderate stress levels, as induced by the employed negative pictures, NE binds well to alpha-2 receptors which is associated with a beneficial influence on PFC function (Arnsten, 1997). It is hypothesized that in this case the processing of irrelevant sensory

information is inhibited in the OFC and that arousing stimuli selectively enhance postsynaptic gating by increasing NE outflow from the LC to the OFC. PTSD patients have been sensitized by previous acute stressful experiences and enduring chronic stress. The described response cascade to threatening cues like the employed negative pictures is exaggerated. The altered reactivity of the NE-system with its selective effect on postsynaptic gating in the PFC results in a heightened neuronal response to threatening cues. The mutual interaction between the NE-system and the HPA-axis further promotes this selective processing of aversive stimuli in the long-run. NE has an excitatory influence on the HPA-axis. Noradrenergic projections stimulate the nucleus paraventricularis of the hypothalamus (Sawchenko, 1982). This is the region where CRF is synthesized. Whereas the NE-system responds immediately to stressful stimuli, the HPA-axis responds some minutes later but its response is more prolonged. Thereby CRF-mediated plastic changes in amygdala and OFC systems are induced that increase excitability (Rainnie, 2004). CRF has also been shown to increase the firing rate of NE secreting neurons in the LC in a dose dependent fashion (Valentino, 1988).

Altogether, the traumatic event has initiated acute and chronic alterations of the NE and CRF systems. The responsivity of both systems is increased, which strongly contributes to the hyperarousal symptoms in PTSD. The detection of threatening stimuli immediately activates the LC that secrets NE to the amygdala and OFC, thereby increasing their responses to these stimuli. Plastic changes in receptor sensitivity, mediated by chronically elevated CRF concentrations, further contribute to the hyperexcitability of the amygdala and OFC. Threatening stimuli will be preferentially processed, which contributes to the maintenance of hyperarousal symptoms.

8.2.4 Detection of potential threats is fast in PTSD

The described model of a hypersensitive alarm system in PTSD is supported by other studies. Rauch (2000) and Shin (1999) demonstrated that PTSD patients show a highly exaggerated amygdala and OFC response to aversive pictures, relative to controls, indicating the hyperresponsiveness of the alarm system in this population. However, the studies to date have mainly employed imaging techniques that do not

allow any predictions about the temporal characteristics of this alarm response in PTSD. The present study, together with the study by Junghoefer, are the first studies that investigated the rapidity of this hypersensitive alarm response in PTSD. Junghoefer identified a time interval from 60-110ms. The time range identified in the present study was from 90-120ms and thus very similar. A detailed visual analysis of the pictures is unlikely to have occurred at this time. Rudimentary visual cues seem to be sufficient for an emotional appraisal. The pathway for this visual information is outlined in the Liddell model (2005). The retina projects to the superior colliculus in the brain stem. From there the information is passed to the thalamic pulvinar and further to the amygdala and the LC. The LC is concerned with the general alerting complex (Posner, 1997). In response to threatening stimuli the LC releases NE that affects the amygdala and frontal brain areas, including the OFC. NE results in an enhanced activation of inervated brain areas. The frontal areas are concerned with the further evaluation of the stimulus and with the generation of an adaptive behavior. In response to a threatening stimulus a fight/flight response is initiated. The whole process is automatic and not dependent on focussed attention or detailed cognitive processing.

The initiation of a fight/flight response can be best investigated by recording autonomic functioning. Pitman et al. (2001) showed that current PTSD patients show significantly higher heart rate, skin conductance, and electromyogram responses during imagery of their traumatic event. Similar results were found by Shalev et al. (1997). It has to be stated that most studies find similar levels of baseline autonomic parameters in PTSD compared to control subjects. Exaggerated reactivity is rather demonstrated in response to internal or external trauma-associated cues (Orr, 1997). No behavioral or autonomic parameters were assessed in the present study. Future studies could profit from the combined parallel recording of peripheral fight/flight reactions and corresponding processes in the central nervous system. Thereby processes in the CNS could be correlated directly with autonomic or behavioral responses and this correlation can provide some clues to the function of CNS activations. One such study was done by Matsuo et al. (2003). PTSD patients' PFC was investigated with near-infrared spectroscopy (NIRS) while they watched trauma-related visual stimuli. At the same time skin conductance and heart rate were monitored. Along with an increase of oxyHb and a decrease of deoxyHb, indicating increased prefrontal activity, enhanced SCR and heart rate were observed.

8.2.5 Early OFC activation as a diagnostic tool in the assessment of PTSD

The early OFC activation demonstrated in the present study might be used as an additional objective psychophysiological diagnostic criterion of PTSD. Furthermore, the high correlation of the early orbitofrontal source strength in response to negative pictures and the severity of arousal symptoms as assessed with standardized questionnaires like the PDS, validates the common diagnostic methods used in clinical settings. The early initiation of the alarm system might be specific for PTSD, although further studies are needed that investigate the same processes in other anxiety disorders like simple phobia, where specific stimuli can elicit anxiety. Nevertheless it is likely that PTSD is the only disorder characterized by an early hyperresponsive OFC response to threatening stimuli. PTSD has the unique feature that its origin is a traumatic experience. A range of known and unknown stimuli from a variety of sensory modalities have been associated with the traumatic event and serve as future triggers of intrusive recollections. The representations of these stimuli are stored in memory and they influence the emotional perception of environmental stimuli. The alarm system in PTSD is fine-tuned for the rapid detection of potentially threatening stimuli. The high degree of generalization with regard to trigger-stimuli discriminates PTSD from simple phobias. In phobias, usually only one single stimulus is fear-evoking and phobics are not characterized by a general hyperarousal. The early exaggerated OFC activity in response to aversive pictures might be a more valid discriminating diagnostic feature of PTSD than other peripheral measures. Furthermore, the decrease of early OFC activation could serve as an indication of therapy success. The reduction of hyperarousal symptoms should be correlated with reduced OFC activation. OFC activity can easily be measured with EEG or MEG. For the parallel assessment of underlying subcortical activations in the amygdala, other imaging techniques like PET or fMRI would have to be used, but these techniques do not allow the assessment of the early responses that occur around 100ms.

8.2.6 Implications for the prevention and therapy of PTSD

The early activation of a hypersensitive alarm system in PTSD has implications for therapy. Assuming that the basis for the hypersensitivity are alterations in the NE-

system and HPA-axis that lead to a heightened excitability of the amygdala and OFC, noradrenergic antagonists should be effective in the treatment of PTSD. Several studies have been performed that applied the alpha-1-adrenergic antagonist prazosin. Taylor et al. (2002) prescribed to six PTSD patients prazosin and observed a marked improvement of sleep functions. Patients particularly reported less nightmares. When the same medication was given during the daytime, emotional distress after completion of an emotional stroop task that included a trauma-related word list was reduced compared to a placebo control group. Moreover, in a two-week follow-up, a reduction in global PTSD illness severity was found (Taylor, 2006). It is likely that the patients investigated in the present study would show a weaker OFC response to the aversive pictures after application of prazosin.

Clonidine is another pharmacologic agent that suppresses the release of NE. It has been proven useful in the reduction of hyperarousal, hypervigilance, sleep disruption, exaggerated startle response, nightmares, and behavioral irritability (Kolb, 1984; Kinzie, 1989). Further studies investigated the effects of propranolol, a nonselective beta-adrenergic blocker, in the acute aftermath of the traumatic event (Pitman, 2002; Vaiva, 2003). Vaiva et al. compared 11 trauma victims that either experienced motor vehicle accidents or physical assault and were treated with propranolol starting 2-20 hours after the trauma, with a matched group of 8 victims who refused propranolol. Two months after the event a higher PTSD prevalence was found in the no-medication group. Similarly, PTSD symptom scores were higher in the untreated sample. The authors concluded that the physiologic adrenergic-induced arousal during the traumatic event and in the acute post-phase leads to increased brain plasticity that results in the outlined neuronal hyperexcitability and hypersensitivity of the NE-system. The treatment with propranolol is assumed to inhibit these plastic changes and thereby it can help mitigating PTSD symptoms and it might even prevent PTSD. Similar results were found by Pitman who investigated the effects of propranolol on the development of PTSD and patients' physiological reactivity to internal trauma cues three months after the event. In a double-blind, placebo-controlled study, propranolol was given to subjects not longer than 6 hours after the traumatic event, in the majority of cases motor vehicle accidents. After one month the PTSD rate was 30% in the placebo group and 10% in the propranolol group. After three months, subjects listened to tape-recorded scripts of their traumatic event and they had to imagine this event for 30 sec. Heart rate, skin conductance,

and electromyograms were measured. It turned out that zero of eight propranolol, but six of 14 placebo subjects were physiologic responders in this task. It was concluded that propranolol treatment starting ideally within a few hours after the traumatic event might have a protective function and might prevent the development of PTSD and reduce symptom severity.

Altogether, these pharmacologic treatment studies demonstrate that the use of (nor)adrenergic antagonists is a promising approach to treat arousal symptoms. It might even prevent the development of PTSD. Abnormal arousal processes start early in the information processing of PTSD patients. This was shown by the early OFC activation in response to the initial exposure to threat-related stimuli. In the present study this effect was observed to start 90ms after stimulus onset. The early activation of the alarm system might influence all further processing stages, for example by directing attention selectively to threat-related information, or by selectively enhancing memory consolidation for aversive material.

8.3 Lack of repetition suppression in PTSD

The healthy German control group in the present study showed a suppression of neuronal activity in response to the repetition of negative pictures in inferior prefrontal and anterior temporal areas. Significant activity reductions were found bilaterally comparing the first with the third picture presentation. In frontal areas a significant suppression was already observed comparing the first and second presentations. The effect was specific for negative stimuli. No activity suppression was found for positive or neutral slides. These findings are consistent with several earlier studies of repetition suppression (Ringo, 1996; Buckner, 1998; Ishai, 2004). The effect was limited to negative pictures, which corresponds with findings by Ishai (2004) and Bentley (2003) showing strong effects particularly for fearful material. Furthermore, the identified time interval for repetition suppression was 230-380ms after stimulus onset, which corresponds well with the MEG study by Penney (2003) who found activity reductions between 250-350ms. Similarly, the peak of repetition suppression in the study by Begleiter (1993) was around 240ms. The PTSD group was characterized by a bilateral lack of repetition suppression. Rather, in left-sided inferior frontal areas a significant amplitude increase was found from the first to the third

presentation of negative pictures. Similarly, a trend for an augmented amplitude across presentations was observed in anterior temporal regions. Although the Kurdish control group did not show pronounced suppressive effects, the tendency was in the direction of an amplitude reduction across presentations of negative pictures. The group of Schizophrenic patients was characterized by a generally and extraordinarily high amplitude for all picture presentations. A slight amplitude increase was found in right-sided inferior frontal areas from the first to the third presentation of negative pictures. Otherwise the pattern was similar to the other two control groups. The particularly high source strengths in the Schizophrenic control group may be an artefact of a reduced signal-to-noise ratio compared to the other groups. ERP responses are a function of changes in phasic neural firing on the one hand and background activity on the other hand. Two factors may be considered to contribute to a reduced signal-to-noise ratio in Schizophrenia. First, with regard to background activity it has been demonstrated that Schizophrenia patients show more low frequency brain activity than healthy controls (Clementz et al., 1994; Winterer et al., 2000). This is likely to be further fostered by neuroleptic medication (e.g. Chung et al., 2002). Second, these patients show aberrant neural synchronization in response to steady-state stimulus presentations (Clementz et al., 2004). Consequently, the signal-to-noise ratio is reduced. The Minimum Norm then has to model the additional noise and thereby attributes more energy to the source.

However, the strong prefrontal activation in the Schizophrenic patients gives rise for the discussion of a particularly intriguing aspect of Schizophrenic psychopathology that shall be addressed here in a brief excursion: many authors have argued that the PFC of Schizophrenic patients schows disturbances. This can be seen for example in the debilitating symptoms of cognitive disorganization and partial loss of volition. The PFC is the site where representations of behaviorally salient rewards and associated goals are maintained. The PFC plans and organizes action sequences that are required for goal attainment and it initiates adequate behaviors. To fulfil this function, the PFC is dependent on afferent inputs that guide the updating of goal representations in an ever-changing environment. An organism is thereby thought to seek for the maximization of positive reward. Stimuli that signal a higher subjective salience gain priority. According to the dopamine gating hypothesis, phasic dopamine bursts ‘open the gate’ for afferent signals to the PFC. Thereby dopaminergic transmission links the evaluation of stimuli and the

implementation into actions. In other words dopamine release links the evaluation of a potential future reward and the behavior that is required to receive it. In an animal experiment it was shown that the injection of a dopamine antagonist significantly reduced the active approaching behavior of a rat to receive a food reward, although the actual consumption of food was not altered when the rat was placed close to it by the experimenter (Ikemoto, 1996). This finding demonstrates that the subjective salience of a stimulus is not changed by decreased dopamine levels, but what is changed is the active behavior to obtain the reward. Although the effective treatment of Schizophrenic symptoms like halluzinations with dopamine blockers has led to the theory that the disorder is characterized by a general hyper-dopaminergic state, it is hypothesized that the prefrontal cortex is characterized by reduced dopamine activity. This is supported by the resistance of symptoms like cognitive disorganization against antagonistic dopaminergic medication (see Montague, 2004). The presented ideas are particularly relevant in light of the symptom of flattened affect or the often assumed 'insensibility' of Schizophrenic patients when confronted with affective material like the emotional pictures employed in the present study. These symptoms might be present on a behaviorally level, but the findings from the present study may be interpreted in the way that this is not true at the level of the central nervous system. In the present study strong prefrontal activations have been observed in response to affective pictures. Schizophrenics seem to intensively process this kind of material, but due to a lack of the linkage between the action planning PFC and the dopaminergic innervation they can not put this processing into action. For a more detailed description of the role of dopamine in behavioral control see Montague (2004).

Repetition suppression refers to an attenuation of neuronal activity across repetitions of visual stimuli. The effect underlies emotional modulation. Repetitions of threatening stimuli have been shown to result in a stronger suppressive effect than repetitions of neutral stimuli (Bentley, 2003; Ishai, 2004). Repetition suppression is regarded as an adaptive mnemonic filter (Li, 1993). This filter is responsible for the allocation of attention and orientation to new stimuli. At the initial exposure, the summed activity of neurons representing the stimulus is likely to provide a signal to other systems that the currently perceived stimulus is new and deserves attention. When the stimulus becomes familiar across repetitions, the neuronal network representing it becomes 'thinned out' so that only neurons representing essential

features remain active. This in turn reduces the drive on the orienting system and frees processing resources for other, competing cues. Along with this neuronal adaptation goes a behavioral habituation.

8.3.1 Decreased repetition suppression promotes an attentional and orienting bias towards threat-related material

The observed lack of repetition suppression in PTSD is compatible with other studies demonstrating general abnormal stimulus processing in this disorder. Some of the diagnostic criteria for PTSD are disturbed attentional processing and associated hyperarousal, difficulties with concentration, exaggerated startle response, hypervigilance, and autonomic hyperactivity. Kolb (1987) suggested that “in terms of clinical expression and behavior, the individual reverts to a state of hypersensitivity in which a multitude of stimuli, both internal and external, lead to arousal. Recurrent intrusive emotional arousal both sensitizes and further simultaneously disrupts this process related to learning and habituation. With this excessive cortical sensitization, and diminished capacity for habituation, lower brain stem structures …, such as the locus coeruleus escape from inhibitory cortical control”. The associated abnormalities in stimulus processing have been investigated in startle response experiments and event-related potential studies. PTSD patients tend to show significantly greater startle responses to acoustic stimuli as compared to healthy subjects (Butler, 1990). Similarly, Miller (2004) found a pattern of startle modulation in PTSD patients that suggests greater defensive reactivity and reduced visual perceptual engagement. In this study subjects watched emotionally evocative stimuli after exposure to trauma-related and non-trauma-related stressors. These studies are indicative of information processing disturbances in PTSD. An example of an ERP investigation supporting the information processing abnormalities is the study by McFarlane et al. (1993). It is generally accepted that the N2 ERP-component as well as the P3 are delayed when stimuli are harder to discriminate, and that the P3 amplitude is decreased in this case (Näätänen, 1986). McFarlane et al. employed a three-tone reaction-time task where subjects had to press a button when they detected an infrequent tone (target). They further had to withhold their response to an equally infrequent distractor tone and to a frequent common tone. All tones were presented against white noise. Compared to

the healthy control group, PTSD patients showed slower reaction times to the target tones. Furthermore, their N2 was significantly delayed and the P3 amplitude was significantly smaller to both, distractors and targets. Controls showed differences in P3 amplitude to targets and distractors. The findings suggest that PTSD patients had more difficulties with stimulus discrimination. The authors argued that the delayed N2 means that patients spent more time on stimulus discrimination, which is also supported by the longer reaction times. Furthermore, the reduced P3 amplitude together with the fact that this component was similar to targets and distractors, indicates that PTSD patients had fewer perceptual resources available to make a decision which stimulus was the irrelevant one. The conclusion from these results is that PTSD patients have difficulties in processing and differentiating relevant from irrelevant information.

These findings have high relevance for the lack of repetition suppression in the present study. The impaired perceptual evaluation of stimuli finds its expression in the lack of repetition suppression. Attentional resources stay focussed on the threatening stimulus. No adaptation or behavioral habituation occurs, despite increasing familiarity of the cue. The defect in early stimulus gating is responsible for collecting attentional processing and orienting responses to stimuli that are associated with the traumatic event. Contextual information are thereby factored out. The abnormalities of attentional processing and orienting responses in PTSD are further supported by observations of unusual eye-movement patterns after the presentation of target stimuli in the study by McFarlane. According to some authors (e.g. Rayner, 1978), eye-movement patterns reflect an additional valid measure of attention. In order to investigate attentional bias in PTSD, Bryant et al. (1995) measured eye-movement and fixation in PTSD subjects when they were presented threat-related or neutral words together with filler words. Three filler words were always parafoveally presented in parallel with one neutral or threat-related word. Subjects were instructed to look at the words in any manner they wished. The authors found that patients fixated on the threat words more than on neutral words. Control subjects on the other hand did not differentiate between threat and neutral words with regard to initial fixations. Furthermore, PTSD patients had a higher percentage of orienting responses in general and on threat trials in particular compared to controls.

Additional support for selective processing comes from the studies by Bryant (1997) and Chemtob (1999). Bryant demonstrated a visual attention bias to threat stimuli in PTSD when subjects performed the dot-probe task. Likewise, Chemtob observed that the presence of a trauma-related stimulus interfered strongly with a concurrent digit detection task. Subjects were not able to disengage their attentional resources from the distractor slide to perform the digit task. Accordingly, Shalev et al. (1992) argued that PTSD patients are likely to show perceptual abnormalities and an inability to ignore stimuli that have lost their novelty. In their study they compared the physiologic responses to loud startle tones in a group with PTSD, a traumatized non-PTSD group, a group of patients with other anxiety disorders, as well as a healthy control group. The PTSD group was the only group that showed a lack of habituation in the skin conductance response. The usual adaptation to reoccurring aversive tones did not take place in the PTSD patients. A lack of repetition suppression is in line with these observations. The defect in early stimulus gating with the accompanying attentional focus biased towards threatening stimuli and the difficulties in differentiating relevant and irrelevant information may contribute to the phenomenons of hyperarousal and also of flashbacks. Whereas in healthy subjects repetition suppression facilitates new objects to be identified due to the freed processing resources after familiar stimuli have been dealt with, this integration of new contextual information is hampered in PTSD. In these patients, attention and orientation stay focussed on the threatening stimulus due to the non-adaptive mnemonic filter. This leads to an enduring activation of the alarm system and results in sustained arousal. Furthermore, this threat-focus can easily contribute to the triggering of intrusive flashbacks that are characterized by a lack of integration of the current (usually safe) context.

The lack of repetition suppression in PTSD is responsible for keeping attentional resources occupied with the threatening stimulus. Patients stay oriented towards this cue. This idea is compatible with the findings from Paunovic et al. (2002) who demonstrated an attentional bias for threat-related material in crime victims with PTSD. In a supraliminal Stroop task, subjects had to name the color of various trauma-related, positive, and neutral words. As compared to controls, the patient group showed a marked interference effect when color-naming trauma-related words. Response latencies were significantly longer in patients. As suggested by Foa (1998), the Stroop interference is due to the activation of the pathological trauma

memory structure. In a later free recall task, PTSD patients were characterized by an explicit memory bias for trauma words. Together these findings were interpreted as PTSD subjects having an attentional bias towards threat-related material. Another study by Harvey et al. (1996) extends the findings from the supraliminal Stroop task to a subliminal version. Thereby it is proposed that also the preattentive processing of information is biased towards threatening stimuli. In the study by Bryant (1995), not only attention was more strongly directed towards threat-stimuli, but in addition PTSD subjects showed generally more orienting responses to new stimuli than controls and these were most pronounced when threat words were displayed.

PTSD patients' preoccupation with environmental stimuli that represent their trauma concern was also found by Dalgleish et al. (2001). They used the attentional dot probe paradigm to investigate visual attention of children and adolescents with PTSD. In this task word pairs are briefly presented on a screen, one word above the other. In the critical trials one of the words is a threatening one and the other is neutral, otherwise both words are neutral. Briefly after the word presentation a dot probe appears in a place previously occupied by one of the words. Subjects have to respond via button press as quickly as possible when the dot probe appears. It is supposed that subjects show faster reaction times when the dot appears at the location of the word they preferentially attended. The study results yielded a greater attentional bias towards threat-related information relative to control subjects. It has to be noted though that two different types of threat-related words were used, namely social-threat-related and physical-threat-related words and the visual attentional bias in that study was in favour of social-threat words. The authors hypothesized that attentional bias can be specific to personally relevant concerns. Social-threat might be the main concern of the tested subjects because many of them had experienced interpersonal violence. Other studies have not found such a threat-differentiation (e.g. Vasey, 1996).

The described bias in visual attention in PTSD subjects has already been described in Beck's theory (1985). In this model anxious individuals are characterized by cognitive 'threat schemata' that are specifically related to the processing of threat-related stimuli. PTSD subjects with their symptomatic hypervigilance are especially prone to this information intake in favour of schema-congruent threatening environmental cues. The lack of repetition suppression, when repeatedly confronted with the same aversive pictures, is in line with this highly selective information

processing. Attentional resources are focussed on threat-related stimuli without adaptation. A negative stimulus will be processed as if it stays 'novel' even after repeated exposure to it. The abnormally working mnemonic filter in form of a lack of repetition suppression demonstrated in this study can be regarded as a neuronal correlate of the maladaptive heightened perception of danger in PTSD. It represents an important factor in the etiology and maintenance of the disorder. A vicious circle is manifested starting with anxiety that leads to an enhanced vigilance for threat. The sensitized threat detection system in turn increases anxiety and thereby hypervigilance. Additionally, the present study has shown that the degree of the reduction of repetition suppression is correlated with overall PTSD symptom severity. The more affected a patient is by PTSD symptoms, the stronger is the lack of repetition suppression in anterior temporal brain areas.

One critical issue regarding the discussed lack of repetition suppression has to be considered. When looking at Figure 18 b, it might be argued that the lack of repetition suppression in the PTSD group might be due to a lack of initial response activation to the first presentation of negative pictures. Control subjects show a clearly higher source strength in left-sided inferior frontal and anterior temporal areas in response to the first presentation of aversive slides, compared to the PTSD patients. At first sight this finding seems counterintuitive. It could have been expected that PTSD subjects would show the highest initial source strength. A possible explanation for the present result might be the following: as has been demonstrated, PTSD subjects' response to the first viewing of negative pictures is an early orbitofrontal source strength increase in the time interval from 90-120ms. It has been argued that this is indicative of a hypersensitive amygdala-based alarm system. It is possible that this subcortical response interferes with subsequent inferior frontal and anterior temporal neuronal activation, resulting in a response inhibition. Masking experiments (Morris, 1999) have demonstrated that conditioned fearful visual stimuli that have been previously paired with an aversive tone elicit less activation in the fusiform gyrus and the temporal pole when presented in a masked compared to an unmasked condition. Furthermore, the fusiform gyrus and OFC have also shown a negative covariation with the amygdala in the masked condition. This means that subcortical responses to fearful visual stimuli disrupted cortical processes. A similar mechanism might operate in the present case. Although no masking paradigm was used, a strong subcortical involvement in the initial processing of negative pictures is

assumed, derived from the finding of early affective modulation of orbitofrontal activity in the time interval from 90-120ms (see above). These subcortical processes may interfere with the initial response of inferior frontal and anterior temporal areas and lead to a decreased activation. This effect is abolished at repeated presentations of the pictures when picture evaluation is guided more and more by conscious processes and familiarity.

8.3.2 Implications for the treatment of PTSD

The biased attentional processing and orienting responses that contribute to the maintenance of hyperarousal and reexperiencing symptoms have implications for the treatment of PTSD. Patients are often not aware of perceptual cues that serve as triggers for intrusive recollections or sensations. Nevertheless there is a processing advantage and reduced perceptual threshold for these cues. PTSD patients are more likely to notice them in the environment. A wide range of stimuli that need to be only loosely associated with the original traumatic stimulus or with the traumatic situation can trigger intrusions. These can be physical cues that are similar to those present briefly before or during the trauma, or matching internal cues like bodily sensations. As Ehlers et al. (2004) suggest, therapy should comprise an education and training in the identification of these trigger stimuli. It is expected that the conscious perception of these stimuli leads to an orienting response and to the restriction of attention to the stimuli. Normally, this could induce intrusive experiences, because the subject lacks the integration of the current (environmental) context that signals safety. Therefore, in a second step, patients need to learn to realize that the encounter of the threatening stimulus does not indicate danger now. The stimulus occurs in a different context and attention has to be actively guided to these new contextual cues. Patients have to be instructed to pay close attention to these contextual cues. The lack of repetition suppression is a central neural underpinning of the difficulty to shift attentional and orienting resources to non-trauma related contextual cues. The strong focus on the threatening stimulus that is treated as if it is ‘novel’ from a neuronal perspective, even after repeated exposure to it, occupies attentional resources and hinders context perception. This focus further contributes to the activation of the alarm system with the autonomic and behavioral consequences of hyperarousal. The integration of

contextual cues contributes to a more adequate appraisal of the trigger situation: namely that 'now' there is safety, as indicated by the contextual stimulus configuration. Altogether, this should lead to a reduction of reexperiencing and arousal symptoms. A reduction of these symptoms should be correlated with a normalization of repetition suppression. A successful therapy should go along with a suppression of neuronal activity in inferior frontal and anterior temporal brain areas when aversive pictures are repeatedly perceived.

8.4 Selective activation of associative "hot" memory networks

The present study demonstrated a significant amplitude increase in bilateral temporal cortex of PTSD patients from the first to the third presentation of negative pictures. No such increase was found for positive and neutral stimuli. In the healthy German control group a different pattern emerged. No significant increase across presentations was found for negative pictures. Instead, the third presentation of positive cues evoked a significant augmentation of the amplitude in the right hemisphere, as compared to the initial presentation. Like in the PTSD group, no amplitude change was observed across presentations of neutral pictures. In the Schizophrenic patients and Kurdish controls there were no significant amplitude differences between the first and third presentations of any of the picture categories.

The described effects were found in the time interval from 380-600ms. This time range complies well with intracranial depth electrode recordings and scalp recorded ERP recognition memory studies that found repetition modulation of the N400/P600 ERP complex in the temporal lobe. The time window starting at approximately 400ms after stimulus onset and lasting up to roughly 600ms after stimulus onset and beyond, is typically related to visual recognition memory effects in respective designs.

As expected, activity enhancing effects were found only when the first and third picture presentations were compared. The first and second presentations were separated by only about 11s, whereas approximately 28min elapsed between the first and third viewing of each picture. It has been argued that short-delay effects that are supposed to occur in posterior parietal regions, dorsolateral prefrontal cortex, and anterior cingulate, would rather represent access to semantic stimulus

representations. Long-delay effects on the other hand are associated with the targeted activations of sensory-perceptual episodic memory networks and are expected to occur in temporal brain regions (Guillem, 1999).

The temporal lobe constitutes the neural basis for autobiographical memory. Thereby different temporal regions fulfil distinct functions. The hippocampus has been demonstrated to be necessary for the 'binding' of episodic memory contents. It is further responsible for the generation of the temporal and spatial context of these memories. The amygdala accounts for the emotionality and in addition it modulates the activity of sensory-perceptual cortex. According to Conway's model (2001), episodic memory that represents the lowest level of the 'framing' autobiographical memory is characterized by vivid internal pictures of life events that are generated by the same cortical areas that are responsible for the initial perceptual processing. The temporal cortex comprises the visual ventral processing stream that also stores representations of visual objects. The retrieval of sensory-perceptual representations of personal life events is associated with the activation of these areas which leads to the 'experience-near', highly sensual nature of the recollection. The recollection of emotionally salient events goes along with an amygdala-mediated enhanced arousal of temporal cortex. The retrieval of sensory-perceptual episodic memory (which is compatible with the concept of the "hot" memory system by Metcalfe and Jacobs, 1996) can be triggered by stimuli that have some resemblance with aspects of the original scene.

8.4.1 The present findings in the light of Lang's bioinformational theory of emotion

In general, the present findings from the healthy German controls and the PTSD group that showed an amplitude increase to repetitions of different sorts of emotional stimuli in the temporal cortex, corresponds to the commonly reported enhancement of neuronal responses for objects with learned behavioral relevance (Desimone, 1996). During the course of life, an individual is confronted with a huge variety of situations, where he/she is exposed to an even greater amount of diverse stimuli. The usual pattern of interaction with environmental cues follows a stimulus – response – consequence sequence. For the interaction with some stimuli, individuals

are equipped with inherent response schemata. This genetically determined 'preparedness' determines the response and behavior towards a given stimulus without prior experience. However, for the adequate interaction with the majority of stimuli, experiences have to be made. Through the process of learning, an information network is generated that comprises information about the stimulus and about the consequences of different responses to this cue. Punishing or rewarding consequences will guide the evaluation of the stimulus and this information is stored in memory. Affective stimuli are not 'affective' per se but become 'emotionally relevant' for an individual by rewarding or punishing interaction outcomes. Emotional stimuli are usually important for survival and their neuronal representations in the brain are particularly strong. Furthermore, representations of emotional stimuli have strong associative connections to related information units. In the case of PTSD, traumatic life events and associated threatening stimuli have led to the generation of a pronounced autonomous associative fear network, as well as a predominant defensive motivational system. Healthy individuals without traumatic experiences have a less pronounced fear network and their behavior is guided more by the appetitive motivational system, relative to PTSD.

Lang's bioinformational theory of emotion (1994) suggests that emotional episodes are represented in memory as networks of mutually activating information units. The entire network consists of stimulus representations, information about verbal, physiological, and behavioral response programs, and interpretive information about the meaning of the stimulus. Within and between these higher level concepts, associative connections exist. The network is activated when an individual is presented with information that matches some of the network's elements. Visual stimuli that have some resemblance with the stored memory representations are only one example of possible triggers. Depending on the strength of the activation, the entire network may be engaged via activation spreading from one unit to the other. As a result, relevant information from long-term memory are brought to the currently active working-memory. The associative spreading of activation can activate semantic representations, sensory stimulus images, affective states, and response programs. The associative spreading of activation is assumed to happen in an automatic manner and can not be controlled. What is assumed to be a specific feature of the emotional network is its direct connection to the brain's primary subcortical motivational system that is strongly involved in the processing of aversive,

but also of appetitive cues. PTSD patients are pathologically primed for aversive information and in this population, confrontation with matching information reactivates these subcortical circuits that include the amygdala and the LC/NE system. These circuits were also active in the original trauma learning context. Amygdala activity modulates activity in sensory cortex, association cortex, and hippocampus. The entire activity in this distributed network potentiates associated knowledge structures in memory and can lead to the reexperiencing phenomenons. In PTSD, the trauma memory is supposed to be strongly connected to the subcortical motivation circuit due to the high emotional intensity at the time of encoding. Even simple cues can easily gate the access to this stored information. It is further suggested that PTSD patients are generally tuned to, or primed for negative cues, meaning that some degree of arousal is persistent in the fear network. Thus, when confronted with, new affectively negative information is also potentiated. Arguing in terms of Konorski (1967), the appetitive drive system would be inhibited in this case, given a primed aversive system. The aversive and appetitive systems work reciprocally. Engagement of either system inhibits the operation of the other. This latter might explain the finding of the present study that PTSD subjects showed the poorest recognition memory performance for positive pictures. In this group the aversive system has been strongly activated, facilitating the storage or retrieval of negative pictures, and at the same time interfering with processing of the positive slides. Neutral pictures were less affected because they might be less dependent on the motivational drive systems.

The described associative network model helps to explain the current findings of a selective activity enhancement upon the repetition of aversive pictures. It is further useful to explain the relative recognition memory bias for negative pictures in the PTSD sample. The negative pictures match information stored in the sensory-perceptual fear memory network. With repeated exposure to the aversive cues, more and more subunits of the network become active, as demonstrated by the enhanced source strength at the third presentation, compared to first and second presentations. It is supposed that activation spreads through the network and that amygdala activity modulates activation in higher order visual processing areas in the temporal cortex. Thereby episodic memories become activated that refer to the lowest level in Conway's autobiographical memory model (2001). These are memories of the traumatic events that contain highly specific, sensory-perceptual impressions.

8.4.2 Emotional stimuli trigger trauma-related sensory-perceptual memories

Vivid internal pictures are the most common intrusive memories in PTSD. The temporal cortex is the brain structure that is responsible for the initial sensory perception of these cues. It is also active at retrieval of visual information. Evidence for this notion can be found in the reviews by Farah (1989) or Bartolomeo (2002). Furthermore, the memory retrieval of visual information is strongly modulated by emotion (e.g. Dolcos, 2005). Dolcos found significantly enhanced activity in higher visual cortex areas when emotional material was retrieved as compared to neutral. The activity augmentation at the third picture presentation in the PTSD group found in the present study is in line with the hypothesis of emotional modulation of retrieval. PTSD patients' negatively primed fear memory network was triggered by the negative pictures. The strong emotionality of these memories contributes to the activation enhancement in temporal areas. These brain regions represent the long-term memory for visual sensory-perceptual trauma memories that have been activated by the pictorial triggers.

Neurons within the temporal visual cortices are modulated by the amygdala. The viewing of emotionally salient stimuli is associated with enhanced visual cortex activity. Lang et al. (1998) focussed on the visual cortex and determined whether emotional valence or arousal would affect the activity in primary and secondary visual processing areas. Subjects watched emotional (pleasant and unpleasant) and neutral pictures taken from the IAPS (Lang, 1997) while fMRI recordings were done. Pictures differed with regard to their arousal ratings. Pleasant and unpleasant pictures both had higher arousal ratings than neutral slides. Unpleasant stimuli were regarded as slightly more arousing than pleasant ones. Significantly more activity was found in the visual processing areas when emotional slides were seen. This effect was mainly due to arousal. However, women showed a significantly higher activity elicited by unpleasant than pleasant pictures while men tended to respond in the opposite direction. It was concluded that modulating projections from the amygdala to V1 and V2 (see also Amaral, 1992) might be responsible for the enhanced visual processing of appetitive and aversive stimuli.

Vuilleumier et al. (2004) provided direct evidence for the modulatory role of the amygdala on visual processing in humans. Three groups of subjects were investigated. One group consisted of patients who had sclerotic damage to the

amygdala and the hippocampus (AH). A second group comprised patients with intact amygdala but sclerotic damage to the hippocampus (H). Finally, a healthy normal control group was included (N). During an fMRI recording, subjects were briefly presented a pair of either neutral of fearful facial expressions together with a pair of pictures displaying buildings. Face pairs were shown randomly in either a horizontal or vertical position. An attentional manipulation was achieved by directing subjects' focus on either the horizontal or vertical position. Thereby face pairs were attended in some trials and sometimes buildings. On each trial subjects had to decide whether the attended pair consisted of two identical or two different stimuli. All groups showed the typical face-related activation of the fusiform gyrus when faces were presented in task-relevant positions. Independent of attention N and H showed significantly stronger bilateral activity in the fusiform and extrastriate cortices when confronted with the fearful facial expressions compared to the neutral faces. This enhanced cortical activity to emotional stimuli was not observed in AH. Furthermore, the authors found that the degree of amygdala damage was negatively correlated with the degree of emotional modulation of cortical activity by the fearful pictures. The advantage of combining lesion and fMRI methodology is that not only correlative declarations can be made, but causal ones. The findings from this study show that the amygdala is responsible for the enhanced activity in occipital and temporal visual cortex in response to emotional stimuli. Amygdala damage abolishes this enhancement.

The demonstrated activity enhancement in bilateral temporal cortex of PTSD patients in the present study, when repeatedly confronted with negative pictures, is thought of representing spreading activation in the sensory-perceptual fear memory network. As part of this process, arousal in the higher order visual areas of the temporal cortex is intensified. It is assumed that the fear-related pictures triggered the fear memory network in PTSD patients. These memories are highly specific, sensory-perceptual impressions.

A likely mechanism for the enhancement of visual temporal cortex activity is modulation by the amygdala as described by Lang (1988). The outlined studies by Sugase (1999) and Lang (1998) have demonstrated enhanced visual cortex activity in response to threatening stimuli. Moreover, firing rates of the amygdala were increased when subjects were exposed to such stimuli (Pascoe, 1985). Vuilleumier (2004) provided a direct link between amygdala activity and emotional modulation of

cortical activity. In line with these findings is the correlation between the degree of activity increase and arousal symptoms found in the present study. The higher the arousal symptoms, as assessed with the PDS, the bigger was the change in source strength in left temporal areas. It can be speculated that the modulatory influence is achieved by cholinergic projections to the cortex. Earlier studies (e.g. Kapp, 1994) showed that cholinergic antagonists attenuate EEG desynchonization, meaning that cortical arousal decreased. Although in the present study PTSD arousal symptoms were a good predictor for the described activity increases in the temporal cortex of patients, so was the severity of reexperiencing symptoms. Severity of reexperiencing symptoms could even explain slightly more of the variance of the activity enhancement, as revealed by regression analyses. It seems plausible that subjects who show the strongest activity enhancement in higher visual processing areas upon the repeated viewing of traumatic trigger stimuli suffer the most from reexperiencing symptoms. In these patients the assumed spreading of activation in the fear network seems to be most easily achieved. Reexperiencing symptoms are most of the time characterized by internal visual sights of the traumatic event. Visual intrusions are the most common, whereas thoughts are rather uncommon, independent of type of trauma (Ehlers et al., 2002).

Symptom provocation studies that measured brain function during script-driven imagery demonstrated a relationship between reexperiencing symptoms and activity increases in visual brain areas, thereby supporting the present correlative findings. Shin et al. (1999) found stronger regional CBF increases in the anterior temporal poles of sexually abused PTSD patients, compared to abused non-PTSD subjects, when they imagined contents of the traumatic event. PTSD patients also had higher increases in self-rated arousal. Rauch et al. (1996) used a similar script-driven imagery symptom provocation paradigm in a group of PTSD patients with a variety of traumatic events. When comparing the imagery of neutral versus traumatic scripts, the traumatic condition was characterized by rCBF increases in brain structures that mediate intense emotion (for example amygdala), in anterior and medial temporal areas, and in secondary visual cortex. Patients reported that the emotional state achieved in the traumatic condition was mainly due to visual mental imagery. All subjects reported intense reexperiencing phenomena. The authors concluded that the activation of higher order visual brain structures may underlie the reexperiencing symptoms in PTSD. Traumatic memories are characterized by their

perceptual and affective quality and they intrude as emotional and sensory fragments. The findings from the present study lend further support to the idea that exposure to cues that resemble aspects of the traumatic event results in fear network activation. The same emotional network is supposed to produce the typical reexperiencing symptoms.

In the healthy German controls a significant right-sided amplitude increase was found for positive pictures. The fact that this effect is localized in the right hemisphere is in line with studies demonstrating that in normal subjects the right hemisphere is more involved in visual processing than the left (Benton, 1979; Junghoefer, 2001). Compared to the PTSD group, it might be that in the controls the appetitive motivational system is more strongly involved than the defensive system. It might be argued that the positive pictures are subjectively more relevant for controls and prompt more extensive activity in higher order visual areas, because they more frequently activate more strongly elaborated visual perceptual associations. Some support for this view comes from a study by Bradley et al. (2003). The authors demonstrated a generally stronger increase of activation in visual association cortex when healthy subjects viewed pictures of different affective content compared to neutral contents. However, the strongest signal change was found for the subcategory of pleasant erotic pictures with a high appetitive motivational relevance, though the difference between this picture type and threat or mutilation pictures, with similar arousal ratings, did not reach significance. Like for aversive pictures, the enhancing effect on higher visual processing areas is assumed to be achieved by projections from the amygdala. For the present study it is suggested that the described effect in the control group is attributable mainly to the high arousing erotic pictures, too, and not to the positive pictures in general.

The present study found a stronger left-hemispheric effect of activation enhancement from the first to the third picture presentation in the PTSD group, which is compatible with findings from Ishai et al. (2000). The authors found that activation during imagery evoked stronger responses in the left, whereas perception of the same stimuli evoked stronger responses in the right ventral temporal cortex. During the first two picture presentations, patients were occupied more with the perception of the slides. About half an hour later, internal imagery of their own past events is likely to be stronger.

8.4.3 Psychopathology modulates brain activity in response to emotional stimuli

The differential enhancement pattern in form of increased activity upon repetition of aversive pictures in PTSD and of appetitive stimuli in healthy controls, can be regarded as being driven by psychopathology. Different forms of emotionality characterize these two groups. These have modulating influences on the reactivity to emotional stimuli. Canli et al. (2001) were the first authors who investigated how the personality traits of extraversion and neuroticism moderated brain activity in response to emotional stimuli. Both of these traits are associated with different emotional experiences (Costa, 1980). Extraverted individuals are characterized by a tendency to be upbeat, optimistic, they enjoy social contact, and they report more positive emotions in everyday life. On the other hand a high degree of neuroticism is manifest in a tendency to worry, to be anxious and apprehensive, and these individuals report more negative emotions in everyday life. Parallels can be drawn to the two groups of healthy German controls and PTSD patients in the present study. Controls are thought to show a greater degree of extraversion, whereas patients share many of the characteristics of individuals with a high neuroticism score. Canli et al. showed alternating blocks of emotionally positive and negative IAPS pictures to participants with varying degrees of extraversion and neuroticism and measured brain reactivity with fMRI. Negative correlations were found between the scores for the two personality traits. The level of brain activation to positive pictures in frontal, right temporal, and subcortical (amygdala) areas was significantly correlated with the degree of extraversion. Contrary, brain activation to negative pictures was significantly correlated with neuroticism scores in left frontal and temporal cortex. All correlations were strong and had coefficients greater than .70. Thus, different values on extraversion and neuroticism are associated with whether a specific brain region will show relatively greater reactivity to positive or negative stimuli, respectively. The authors interpreted these differences in brain reactivity in terms of processing biases that might be based on prior experiences. They also related the findings to the model of two motivational systems (Gray, 1987). The first is the behavioral inhibition system that regulates aversive motivation, the other is the behavioral approach system that is responsible for appetitive motivation. The findings from the present study are in good accordance with the results by Canli. PTSD subjects showed the biggest amplitude

increase in the left temporal cortex upon repetition of negative pictures, whereas healthy controls showed enhanced right-sided activity upon repetition of positive pictures. The lateralization effect is also in good agreement with Canli. In their study the temporal cortex was associated with significant correlations for extraversion in the right hemisphere, and for neuroticism in the left. PTSD patients in general do not exhibit a great amount of approaching behavior, but instead show defensive reactions or withdrawal as typical diagnostic symptoms. Neuroticism has been associated with PTSD in several studies (Cox, 2004; Talbert, 1993) and some authors even found that neuroticism is a risk factor for the development of PTSD (Engelhard, 2004). For the healthy German controls a positive correlation was found between non-clinical BDI depression scores and amplitude increases in response to negative pictures. This correlation further strengthens the idea that a subjectively experienced negative emotionality promotes a biased information processing towards negative material. The present study did not assess explicitly the level of extraversion and neuroticism in the participating subject samples. Since personality traits have an influence on brain reactivity to emotional stimuli, future studies should assess relevant personality traits, with a special focus on the specific personality alterations that occur in chronic PTSD.

Schizophrenics in the present study did not show any significant amplitude increases in temporal areas across repetitions of any of the picture categories. There are two possible reasons for this observed lack of affective preference. Schizophrenic patients are characterized by poorer sustained attention (e.g. Ito, 1997) that could affect emotional differentiation. However, the performance on the recognition task argues against this idea. If attention was impaired, one would expect weaker memory performance, too. Yet, Schizophrenic patients did not differ from the other two control groups with regard to their recognition performance. Another explanation might be more fruitful. These patients might suffer from a general deficit in the discrimination of emotionally salient pictures. Some support for this hypothesis comes from two recent studies from our own lab. Rockstroh et al. (in press) replicated the finding of differential brain responses when healthy control subjects watched emotionally arousing (pleasant and unpleasant) pictures. Larger posterior brain responses were found for arousing stimuli compared to neutral ones in a RSVP paradigm. Contrary to controls, this distinction between emotionally and neutral pictures was marginally in Schizophrenic patients. This finding was related to less differential activation in

limbic, prefrontal, and visual brain areas (Takahashi, 2004). In that study, reduced activation was found in emotion-sensitive brain areas when patients watched affective pictures, as compared to healthy controls. Gooding (2001) demonstrated a reduced perceptual bias in response to emotional facial cues. Corresponding results of reduced emotional differentiation in Schizophrenic patients were found in an earlier study from our lab (Saleptsi, 2005), when longer stimulus presentations (2s) were used in an IAPS design. The present findings lend further support to the hypothesis of a deficit in affective distinction in Schizophrenia.

The Kurdish control subjects did not suffer from any psychiatric disorder, but nine of ten subjects reported at least one traumatic life event. Despite this autobiographical episode, this group did not show a significant amplitude increase in the temporal cortex upon repetition of negative slides. This can be interpreted in favour of the specificity of a pronounced and sensitized associative fear memory network in PTSD. The experience of traumatic life events does not automatically lead to the development of a maladaptive fear network. It should be considered, however, that the PTSD group had experienced more severe and a greater number of traumatic events than the Kurdish control group. According to the building-block effect (Neuner et al., 2004) the number of traumatic events predicts the psychological strain. The underlying brain mechanisms are supposed to be more affected, too. This could contribute to the observed differences in amplitude change.

8.4.4 Facilitation of recognition memory for threatening stimuli through association learning

The present study found a relative recognition memory bias for threat-related material in the PTSD group. Patients did not differ in their negative picture recognition performance from the three control groups but were severely impaired on the positive and neutral pictures. The PTSD group showed the best performance in recognizing negative pictures. The three control groups performed equally well on the recognition of all three picture categories, thereby showing no memory bias for negative information. This group difference was not due to differential response biases as indicated by similar C-scores for the respective picture categories across all four groups. Nevertheless, all groups were most confident in keeping apart negative

targets and distractors as compared to the positive and negative conditions. According to Rugg et al. (2003) recognition performance is based on a conscious, explicit recollection and on an implicit process of the experience of familiarity, induced automatically at the reoccurrence of the stimulus. Thus, the present findings are in line with the results of Zeitlin et al. (1991) and Golier et al. (2003). Zeitlin tested explicit and implicit memory in Vietnam combat veterans with and without PTSD. Subjects had to encode combat, social threat, positive, and neutral words either elaboratively by indicating their liking of each word on a seven-point scale, or nonelaboratively by counting the number of letters in each word. Explicit memory was tested in a later cued recall task and implicit memory via a word completion test. In the cued recall task, both groups did not differ in their recall of combat or social threat words, but patients performed significantly worse on positive and neutral words. This indicates that PTSD patients suffer from a generally poorer explicit memory, except for threat-related material. This effect was independent of the encoding condition. In addition, a correlation was found with the extent of combat exposure. These findings correspond well to the complaints by PTSD patients that they have difficulties with concentration and memory problems in general, yet they easily recall trauma-memories. In the implicit task, patients completed more combat-related words than any other word type and more than controls. Performance for the non-combat-related words was similar in both groups. This effect was slightly more pronounced in the primed than in the unprimed condition. The implicit memory bias towards trauma-related material was correlated with the severity of PTSD. The authors concluded that chronically activated and easily accessible cognitive representations of the trauma in memory are responsible for the explicit and implicit memory biases and that these representations contribute to reexperiencing symptoms like flashbacks. Golier et al. employed the paired associates test as a test for explicit memory in a group of 31 Holocaust survivors with a current PTSD. A group of 16 Holocaust survivors without PTSD and 35 Jewish adults not exposed to the Holocaust were included as control groups. Subjects were shown word pairs, half of which were highly associated with each other and the other half was unrelated. Subjects were asked to read them aloud and to memorize them. The first version of the test included only emotionally neutral word pairs. In a second version, the low associate word pairs consisted of a neutral and a Holocaust-related word. High associate word pairs were neutral. At recall, only one word from each pair was presented and

subjects had to produce the associated word. In the low associates conditions, PTSD patients showed a generally poorer performance than the other two groups that did not differ. However, patients showed a facilitation in the recall of trauma-related relative to neutral words. The control groups did not show this relative emotion-related facilitation. In the high associates condition that used only neutral word pairs PTSD patients showed the same performance like the non-PTSD Holocaust group, and their performance was only slightly worse than that of the non-exposed group. The trauma-related facilitation of explicit memory was specific for the PTSD group and was not a general effect of emotional salience. If the latter was true, also the Holocaust survivors without PTSD would have been expected to show this effect, but that was not the case. It was further found that intrusive symptoms were associated with the biased explicit memory for trauma-related material.

Due to the associative character of the trauma-memory, the trigger stimulus itself becomes easily associated or linked with the network and is effectively kept in memory. The active aversive drive system of PTSD patients is tuned for the easy integration of the negative trigger stimuli. As demonstrated in several imaging studies (e.g. Liberzon, 1999; Rauch, 2000), PTSD subjects show exaggerated amygdala responsiveness to general threat-related stimuli. This is accompanied by the generation of strong emotional associations with sensory stimuli. Because of the generalization, the number of new sensory triggers that become associated with subjective negative emotional states, increases. New stimuli become easily linked with the vivid traumatic memories. This may be related to the chronicity of PTSD. This enhanced processing does not work for positive pictures because of the inhibition of the appetitive drive system. Positive pictures are neglected. The aversive and appetitive systems work reciprocally. Engagement of a primed aversive motivational system and episodic memory in PTSD inhibits the operation of the appetitive system (Konorski, 1967). Neutral pictures neither benefit from the active aversive system, nor is their processing strongly impaired by the inhibited appetitive system. Neutral pictures might be less dependent on the motivational drive systems.

The recognition memory bias for threat-related material found in the present and other studies might represent a crucial feature in the maintenance and chronicity of the disorder. In chronic PTSD it has been observed that with time more and more stimuli can serve as triggers for intrusive symptoms. This means that more stimuli become paired with the trauma-memory. This might also lead to stronger avoidance

symptoms. It might be argued that PTSD patients suffer from a severe ongoing disturbance in associative learning. Intrusive symptoms are not only elicited by stimuli that were present at the time of traumatization. Rather, in the course of the disorder, additional associations between stored traumatic memories and new (trauma-related) stimuli are made. On the other hand, a generally poorer explicit memory characterizes PTSD.

8.5 General methodological considerations

8.5.1 PTSD sample

The PTSD patients investigated in the present study were all victims of political persecution. All subjects had experienced multiple (between 3 and 6) traumatic events over an extended period of time. Events included torture and repeated physical abuse in the majority of cases. Their chronic traumas continued for months or even years. The current PTSD diagnosis does not fully capture the severe psychological harm that occurs with such prolonged, repeated trauma. For this type of trauma, the diagnosis of complex PTSD has been suggested (e.g. Herman, 1997; Roth, 1997). The following symptoms of complex PTSD have relevance for the present subject sample: alterations in emotional regulation (for example persistent sadness, suicidal thoughts, explosive or inhibited anger). Alterations in consciousness (like reliving traumatic events, or having episodes in which one feels detached from one's mental processes or body), alterations in self-perception, which may include a sense of helplessness, shame, guilt, stigma. Further alterations are observed in relations with others (including isolation and distrust). Moreover, alterations occur in one's belief system, which may include a loss of sustaining faith or a sense of hopelessness and despair. The majority of investigated patients had a comorbid diagnosis of depression. The findings from the present study are limited to complex PTSD. Future studies have to investigate, whether the abnormalities of emotional processing and memory found in the present patients sample can be found in simple PTSD, too. Simple PTSD usually refers to the pathologic state that can develop after single traumatic events of time-limited duration, like car accidents, natural disasters, and rape.

8.5.2 Stimulus material

The stimulus selection was guided mainly by the two considerations to match arousal scores for negative and positive pictures, and to match all picture categories for the depiction of social content. The second consideration was achieved. Commonly used neutral pictures that depict non-living objects were excluded and replaced by pictures of humans. However, negative pictures were rated as being slightly more arousing than positive ones (M = 5.94 vs M = 4.87). This is due to the fact that pictures of mutilations or of other extremely aversive content have generally higher arousal scores than the most arousing pictures from the positive category (for example with erotic content). Another goal was to include extreme pictures from both categories. However, the problem of different arousal ratings for negative and positive pictures is attenuated by the between-groups design of the present study. Another aspect concerns the fact that picture ratings were not performed by the study subjects themselves. Instead, existing normative ratings of healthy individuals and ratings of a separate group of recruited volunteers that did not take part in this study were used. The entire study protocol was very demanding already and no further load should be put on the participating subjects by the rating procedure. Nevertheless, it would have been especially useful if the PTSD patients in the present study had rated the picture stimuli. In this case the neuromagnetic data could have been analyzed more differentially. Even stronger effects would have been expected when analyses were performed for subsets of pictures subjectively rated as the most disturbing for the PTSD patients. Probably a slightly different subset of the most aversive pictures would have been emerged for each patient, dependent on the subjectively most distressing traumatic event. However, theory predicts a great amount of generalization concerning aversive material that has the potential to elicit distress and intrusions in PTSD. From this viewpoint it is not necessary to differentiate between more or less subjectively relevant negative pictures.

In general, the IAPS is supposed to be a culture-independent set of normative emotional stimuli for experimental research. However, picture ratings have been done primarily by young American psychology students. Only few studies have investigated the assignability of the IAPS to other cultures. These few studies collected normative ratings from various different cultures and compared the results with the original ratings from the US sample. Ribeiro (2005) for example investigated

a Brazilian sample and found that Brazilian subjects generally assigned higher arousal ratings overall. Beside culture-dependent differences in the ratings, also age-related differences have been demonstrated. Backs (2005) found that younger adults rated arousing pleasant pictures as more pleasant and arousing than older adults did. It was suggested that this difference could be explained by greater affect intensity for the younger group and greater emotional control and levelling of positive affect for the older group. The stimulus set employed in the present study has not been evaluated by subjects from non-western cultures and subjects with a non-Christian background. The PTSD patients in the present study were all Kurdish refugees from Turkey except one. All Kurdish participants were Muslims. Different attitudes, for example with regard to sexuality, may influence the evaluation of accordant pictures depicting erotic content. Therefore it would be useful to assess valence and arousal ratings for the IAPS from Muslim subjects.

8.5.3 Stimulus repetition paradigm

The present study employed only two picture repetitions. One repetition occurred after approximately 11s, another after about 28min. The choice of only two repetitions was guided by the effort to include a large spectrum of different picture contents in the three categories, respectively. A large spectrum of different stimuli was important in order to find support for the hypothesis that PTSD patients would show pathology-related abnormalities in brain responses to fear-related material in general with a high degree of generalization. Secondly, a large spectrum was chosen in order to maximize the signal-to-noise ratio that is important for reliable source localization. The employment of further repetitions would have meant that MEG recording duration was significantly longer, which had been unacceptable for the studied patients. However, further picture repetitions at the expense of a smaller variety of different stimuli would allow a better assessment of the temporal characteristics, as well as total degree / gradation of the described suppressive and enhancing effects. The temporal course of the activity enhancing effect in the temporal cortex for example that is supposed to reflect activation of sensory-perceptual episodic memory representations could have been investigated. Continuous activation models assert that activation grows continuously over time (Yantis, 1988). The effect in the present

study was measured after 28min. It might be a lot stronger after a shorter repetition delay. It might be that the present effect was measured when activation spreading was already regressive.

8.5.4 Complementing MEG with fMRI for the direct assessment of subcortical processes

The early activation of the alarm system, the lack of repetition suppression, and the selective long-delay (visual) temporal cortex activation in PTSD are all thought to involve amygdala modulation. Furthermore, episodic memory processes should go along with activation of other medial temporal lobe structures like the hippocampus. In PTSD disturbed hippocampal functions could be expected, regarding the often observed lack of temporal and spatial context of intrusive recollections. Unfortunately, MEG is unable to reliably track subcortical processes or activity in the deeper layers of the brain. Therefore, the findings from the present study should be complemented by recordings from these deeper structures. fMRI would be the ideal method to measure the assumed coactivation of the amygdala and functioning of the hippocampus. However, as outlined above, reliable mapping of amygdala activity is only possible when coronal acquisitions and voxel sizes of 4-8 µl or less are employed (see Merboldt et al., 2001). Such findings would further strengthen the proposed models of emotional processing and memory in PTSD.

8.6 Conclusions

The present study found evidence for abnormal visual processing and recognition memory of affective pictures in PTSD. When PTSD patients are exposed to subjectively relevant threatening stimuli, an emotional appraisal takes place before a detailed visual analysis has occurred. Crude visual information is directly transferred to the amygdala via an extrastriate visual pathway. The amygdala is supposed to be hypersensitive and primed for fear-related material in PTSD patients. The brainstem-amygdala-cortical alarm system is thus rapidly activated in the presence of trauma-relevant cues. This includes a heightened arousal in the OFC that was measured in a

time range from 90-120ms. At this time there is no conscious awareness for the fear-related stimulus. The fast detection of potential threats is important for an organism. This threat detection system is hyperresponsive in PTSD patients and shows an initial activation as early as 90ms after the onset of exposure to a dangerous cue. The early OFC effect is related to arousal, as has been demonstrated by the correlation with PTSD arousal symptoms. Healthy control subjects do not show emotional modulation of early OFC activity.

In the subsequent further stimulus processing, attentional resources are focussed on the aversive stimulus. When repeatedly exposed to a threatening stimulus, controls show a decrease of neuronal responses in inferior frontal and anterior temporal areas in a time interval from 230-380ms. The usual adaptive neuronal response when a stimulus has become familiar due to repeated exposure is impaired in PTSD. In these patients attentional and processing resources stay tuned to the threatening stimulus, despite familiarity. This is reflected in the demonstrated lack of repetition suppression. The more severe the overall PTSD symptom severity, the weaker is the suppressive effect. The preoccupation with the threatening stimulus hinders the integration of other contextual stimuli. This contributes to the maintenance of the disorder.

Threatening stimuli that have some resemblance with features of the original traumatic situation activate a pronounced and sensitized sensory-perceptual fear memory network in PTSD. The spreading of activation goes along with the engagement of temporal brain areas that are concerned with the perception of visual cues. These brain structures also represent the neuronal basis for visual perceptual memories. PTSD patients show the strongest temporal source strengths increases for fear-related pictures in the time range from 380-600ms. Reexperiencing symptoms were positively correlated with this increase. During intrusive recollections the same visual areas that are active at the time of perception become activated. This contributes to the vivid, perceptual and live-like nature of traumatic memories. In the extreme case flashbacks occur that are strongly characterized by these internal pictures that lack a spatial and temporal context. Healthy control subjects that do not have a trauma-related episodic memory had the highest increase in temporal source strength for the subjectively more relevant positive pictures.

In PTSD, new fear-related stimuli that triggered the activation of the fear network, become associated with the network. Thereby the network expands over

time which further contributes to the maintenance of PTSD. PTSD patients can then easily recognize such stimuli in the future. In the present study this was demonstrated by facilitated recognition performance for negative slides. On the other hand, recognition memory for positive and neutral pictures was impaired. Control subjects showed equal performance for all picture categories.

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