University of Konstanz

Department of Psychology

MEG Correlates during Affective Stimulus Processing in Posttraumatic Stress Disorder

Dissertation zur Erlangung des Doktorgrades

Doctor Rerum Naturalium

(Dr. rer. nat.)

Eingereicht an der Mathematisch-Naturwissenschaftlichen

Sektion der Universität Konstanz durch

Evangelia Saleptsi

Gutachter

Prof. Dr. Thomas Elbert

PD Dr. Andreas Keil

□□ρ□ Κ□□□□α□□ί□ο

“…

Ο ουρανός μου είναι βαθύς κι ανάλλαχτος
Ό,τι αγαπώ γεννιέται αδιάκοπα
Ό,τι αγαπώ βρίσκεται στην αρχή του πάντα.

…”

Odysseas Elytis, from: Sun the first

Acknowledgment

This dissertation marks the end of a long journey which began some years ago in Konstanz. I would like to acknowledge the following individuals for their valuable insights, comments and constant support:

I am especially indebted to *Thomas Elbert* and *Brigitte Rockstroh* for their confidence in this project and for giving me the freedom and the time to pursue it. It was an honor and an inspiring and enjoyable experience to do my PhD under your professional supervision. Many thanks to both of you!

The backbone of it all was the fantastic intellectual companionship and the unmitigated joy of working with *Andreas Keil*. He always blows me away with his amazing sharpness, knowledge, and communication skills. Thank you Andreas, for your guidance on this dissertation, I am very grateful!

Sabine Heim was a fantastic colleague and friend who was warm and caring and has been extremely supportive of me. Thank you, Sabin*e,* for being there every time I needed you, for your friendship and support. All the best for your habilitation!

I met *Dana Bichescu* whilst working on my first study. Later on, I shared my thoughts, my coffee and my life with Dana. Dana, thank you for the evening sessions at the ZPR discussing our data and for supporting me with the MEG measurements during weekends. Dana, all the best for your thesis and your life!

I am also extremely grateful to *Victor Candia* for his invaluable feedback on part of this dissertation, for his immediate response to my questions and for being critical of my work. Thanks a lot, Victor, for your advice on how to create amazing figures!

It would be impossible not to specifically thank *Stephan Morrati* for the many fruitful HR and MNE discussions and *Ursula Lommen* for introducing me to the MEG-world and letting me do measurements at the weekends – Ursel, you are great!

I would also like to thank the entire *Clinical Psychology* working group for the enthusiastic and professional atmosphere.

I wish to express my thanks also to *Akis Simos* for his careful reading of and critical comments on the MEG manuscripts at the earliest stages.

I am deeply indebted to all the *participants* of the studies. Without their contribution this dissertation would not have been possible.

Perhaps my biggest stroke of luck was my many friends in Konstanz. Special thanks to all my close friends: Thank you, *Vanessa*, for my best WG-years ever, for the after-the-ZPR sessions and for simply being there for me! Thanks a lot, *Christine*, for the horse-riding sessions, for being so caring through all my ups and downs and for your friendship. Thanks a lot, *Wencke*, *Tobias*, *Jürgen* and *Matthias*, for your friendship!

Many thanks to all my special friends in Greece for supporting me all these years - you mean a lot to me! [illegible]

[illegible]

Finally and most importantly I wish to thank the members of my *family*, who have simply been there for me, and who in many different ways have been daily (despite living in Greece) participants in this dissertation. [illegible]

Konstanz, July 2005

Evangelia Saleptsi

Zusammenfassung

Das Betrachten affektiver Reize löst eine Reihe typischer behavioraler, kognitiver und physiologischer Antworten aus. Die Präsentation affektiver Bilder ist daher eine bewährte Methode zur Untersuchung abweichender affektiver Verarbeitung bei emotionalen Störungen.

Die vorliegende Arbeit setzt sich mit den kortikalen Reaktionen auf angenehme, unangenehme (traumabezogenene) und neutrale affektive Bilder des International Affective Picture Systems (IAPS) mittels Magnetoenzephalographie (MEG) auseinander. Drei Gruppen wurden untersucht: 15 Folteropfer, die, die Kriterien einer posttraumatischen Belastungsstörung (PTBS) erfüllten; 15 Patienten mit schizophrenen Störungen; sowie 12 Kontrollpersonen. Die magnetischen Antworten zeigten keine Unterschiede zwischen schizophrenen Patienten und Kontrollpersonen in den frühen Verarbeitungsprozessen. Für Patienten mit einer PTBS wurde dagegen eine perzeptuelle Erleichterung neutraler Bilder und eine Hemmung unangenehmer Bilder nachgewiesen (N1m Komponente). Ebenso zeigten PTBS-Patienten erhöhte Schreckreflexamplituden und erhöhte Herzraten beim Betrachten angstbesetzter Stimuli. Die späteren Verarbeitungsprozesse konnten in einer anderen Weise differenziert werden. PTBS-Patienten zeigten eine spätere spezifische Erhöhung der Amplitude auf aversive Stimulation sowohl für die frühe P3m als auch für die spätere P3m Komponente. Insbesondere diese affektiven Modulationen wurden auch im Quellenraum nachgewiesen: für frühere Prozesse zeigten PTBS-Patienten eine Hemmung im visuellen Kortex in der Merkmalsverarbeitung traumabezogener Bilder. Die Schwerpunkte der Aktivierung für spätere Komponenten bei PTBS-Patienten (early P3m, late P3m) wurden vor allem an präfrontalen und parietalen kortikalen Hirnarealen identifiziert. Dagegen zeigten schizophrene Patienten und Kontrollpersonen für spätere Prozesse eine Aktivierung in visuellen und in parietalen kortikalen Hirnarealen. Diese Befunde legen nahe, dass PTBS-Patienten die unangenehmen Bilder bereits in der frühen Merkmalsanalyse in visuellen Hirnarealen unterdrücken. In späteren Verarbeitungsschritten, die bei Kontrollpersonen und schizophrenen Patienten von visuellen und parietalen Hirnarealen ausgeführt werden, aktivieren PTBS-Patienten ein präfrontales Furchtnetzwerk für alle erregende Bilder. Auf Grundlage dieser Befunde wird ein Model der affektiven Verarbeitung bei der PTBS entwickelt.

Summary

In the present thesis, study I focuses on the relationship between retrospectively reported childhood experiences and psychiatric diagnoses in adult life, study II and study III covers a wide range of affective stimuli and procedures focusing on special features of emotional processing in PTSD: we implemented a visual paradigm to investigate cortical activation patterns during processing of high arousing (pleasant and unpleasant) as compared to low (neutral) arousing pictures in PTSD patients, in schizophrenia patients and healthy controls using magnetoencephalography; in addition to magnetocortical data we examined subjective ratings, heart rate and startle responses. In studies II and III, standardized colored picture stimuli from the International Affective Picture Systems are used. The neural processing underlying emotional information processing in PTSD patients, in schizophrenia patients and healthy participants is studied and the origin of neuromagnetic activity in the brain is modeled by means of magnetic source imaging (MSI). PTSD patients showed a differential sensitivity for the early time windows for high arousing unpleasant pictures. Avoidance symptoms in PTSD patients were negatively correlated with the difference unpleasant minus neutral for the N1m time window suggesting that amplified responses for neutral pictures were negatively correlated with high avoidance scores. PTSD patients showed for the late components increased activity for high arousing pictures suggesting cortical facilitation in attentional processes. Heart rate responses differed significantly among PTSD patients, schizophrenia patients and control participants showing sustained heart rate acceleration for high arousing unpleasant pictures in PTSD patients. Taken together, the earlier amplification for neutral pictures in PTSD patients such as found in the range of the N1m component may indicate initial cortical inhibition of magnetic fields for visual features that are motivationally significant may be associated with PTSD symptoms. As evidenced by the MNE, high arousing pictures elicited greater activity than low arousing (neutral) pictures did in PTSD patients over frontal and frontoparietal cortical networks for the early P3m window, over anterior and posterior parietal regions for the late P3m window and hereby representing differences among groups. There was evidence of failure in PTSD patients but not in schizophrenia patients to show a specific sensitivity to emotional modulation of visual cortex in the range of the N1m time window. Furthermore, source space projection from subsequent time windows such as early and late P3m revealed specific enhancement of electro-cortical activity in PTSD over prefrontal and parietal cortical areas. This finding may reflect increased allocation of attentional resources to arousing stimuli over time in PTSD patients. Based on these observations elements of a model of human emotional stimulus processing in PTSD is proposed.

Contents

Chapter 1

General Introduction

In the present thesis responses to emotional visual stimuli observed in a sample of PTSD patients, of schizophrenia inpatients, and of matched healthy participants will be investigated and conclusions about underlying response patterns will be drawn. A major theme of this thesis will be to elucidate what is special about emotional information processing in posttraumatic stress disorder (PTSD), emphasizing the cortical areas that contribute to the process. Since the focus of this thesis is on physiological mechanisms, namely magnetocortical activity associated with the visual processing of emotional stimuli, biological aspects will be highlighted, with a strong bias towards magnetoencephalography (MEG), behavioral data, specific autonomic responses (e.g., heart rate responses), and somatic reflexes (e.g., startle responses) collected in an experiment challenging human emotions in a laboratory environment. In addition, the issue of underlying response patterns will be addressed both based on inference from existing knowledge about brain-behavior dynamics and by measuring brain activity with magnetoencephalography.

The rapid pace at which our knowledge of stress processing has expanded over the last decade has led to an increase in our understanding of the psychopathology of PTSD. Taking into consideration data from a variety of research areas, I will also discuss both theoretical and empirical aspects of traumatic stress. I will start with a brief overview of critical issues and theoretical concepts related to stressful life event research and will also present some empirical findings on the relationship between traumatic life events and mental health in adult life.

Of the five chapters presented, one study (study I) focuses on the relationship between retrospectively reported childhood experiences and psychiatric diagnoses in adult life, study II and study III covers a wide range of affective stimuli and procedures focusing on special features of emotional processing in PTSD: we implemented a visual paradigm to investigate cortical activation patterns during processing of high arousing (pleasant and unpleasant) as compared to low (neutral) arousing pictures in PTSD patients, in schizophrenia patients and healthy controls using magnetoencephalography; in addition to magnetocortical data we examined subjective ratings, heart rate and startle responses. In studies II and III, standardized colored picture stimuli from the International Affective Picture System (P. J. Lang, Bradley, M.M., Cuthbert, B.N., 1999) are used. The neural processing underlying emotional information processing in PTSD patients, in schizophrenia patients and healthy participants is studied and the origin of neuromagnetic activity in the brain is modeled by means of magnetic source imaging (MSI).

1.1 Stress and vulnerability to severe mental illness

Modern psychiatry has consistently addressed the seminal role of early childhood experiences in shaping adult behavior. In recent years there has been a growing awareness of the importance of trauma in determining the course of people’s life (Lange et al., 1999; Muenzenmaier, Meyer, Struening, & Ferber, 1993; Mulder, Beautrais, Joyce, & Fergusson, 1998; Read, 1997). Considerable attention has been focused on the impact of the rate of trauma in the general population 56%, (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995), but abundant evidence suggests that high rates of trauma are well documented in individuals with severe psychiatric disorders such as schizophrenia, substance abuse, personality disorders, and depressive disorders and are even more vulnerable to trauma exposure (Saleptsi et al., 2004). Specifically, several studies have documented high rates of trauma in individuals with severe mental illness, with estimates of lifetime rates of interpersonal violence ranging from 51% to 97% (Goodman, Rosenberg, Mueser, & Drake, 1997). Furthermore, surveys indicate that between 34% and 53% of patients with severe mental illness report childhood sexual or physical abuse. These rates of trauma clearly exceed rates reported for the general population (Breslau, Davis, Andreski, & Peterson, 1991; Kessler et al., 1995). Furthermore, compared with other psychiatric patients, those who experienced early adverse events, not only are more likely to attempt suicide, but also have earlier first admissions and longer and more frequent hospitalizations, receive more psychotropic medication and exhibit higher global symptom severity (Briere, Woo, McRae, Foltz, & Sitzman, 1997; Pettigrew & Burcham, 1997; Read, 1997; Read, Perry, Moskowitz, & Connolly, 2001). In studies specifically examining patients with personality disorders, borderline personality disorders has been the most frequently studied in terms of prevalence of early adverse events (Golier et al., 2003). Multiple studies have reported that a history of physical and sexual abuse in childhood has a high prevalence among patients with borderline personality disorders, with some studies finding that abuse is nearly ubiquitous in the early lives of these patients (Golier et al., 2003; Herman, Perry, & van der Kolk, 1989; Zanarini, Gunderson, Marino, Schwartz, & Frankenburg, 1989). Although there is widespread disagreement in reporting trauma events in psychiatric patients, memories of core aspects of severely traumatic experiences generally remain reliable with time (Margo & McLees, 1991; Read, 1997). However, there is compelling evidence that early life stress, such as childhood neglect, physical, or sexual abuse, or early parental loss, constitutes a major risk factor for the subsequent onset of severe mental illness (Saleptsi et al., 2004; B. A. van der Kolk & Fisler, 1994).

A widely held view is that the combination of genetics, early life stress, and ongoing stress may ultimately determine individual responsiveness to stress and vulnerability to psychiatric disorders, such as severe mental illness (Charney, 2004; Mueser, Rosenberg, Goodman, & Trumbetta, 2002; Norman & Malla, 1993; Read et al., 2001; Yank, Bentley, & Hargrove, 1993). The genetic diathesis has largely been demonstrated not by design but inadvertently as researchers have endeavored through selective breeding to develop animal strains that either more reliably or more robustly exhibit the target signs and symptoms resembling a human disorder (Charney, 2004). Because inherited and acquired factors contribute to vulnerability, theoretically the predisposition to illness should be demonstrable by using both psychological and biological measures. Several models have been proposed suggesting that both genetics and psychosocial stress play a causal role in severe mental illness and that multiple brain neural systems contribute to specific functional and structural abnormalities in discrete neuronal networks that mediate the complex symptom pattern in patients with severe mental illness (Mueser et al., 2002; Read et al., 2001). Both inherited and acquired vulnerability to experimentally induced stress have been demonstrated by using animal models.

1.2 Animal models of an adverse life event: early developmental experience versus genetic endowment as determinants of stress vulnerability

1.2.1 Neonatal Stress Models

Given that the pathophysiology of mental disorders remains obscure, a variety of animal research models of stress have been devised to investigate the impact of early life stress on development. Models of early adverse experiences have recently evolved to utilize psychosocial stressors. One approach to studying early life stress by using animal models has been to implement stressors akin to those experienced by adult animals. These models typically stress the young animal by exposing them to noxious stimuli, including thermal extremes, pinprick, foot shock, or surgical procedures and thereby reflect early life stress.

Studies in rats demonstrated differences in hypothalamic-pituitary-adrenal (HPA) axis functioning associated with differences in early experience. For instance, rats exposed to noxious stimuli demonstrated a subnormal HPA axis response during the first 2 weeks of life (De Kloet, Rosenfeld, Van Eekelen, Sutanto, & Levine, 1988). During this so-called stress hypo-responsive period, baseline plasma corticosterone concentrations are lower than normal and are only minimally increased by exposure to a noxious stressor (Sapolsky & Meaney, 1986). It must be that the HPA axis responsivity during childhood is modulated by planned maturational processes, and so that this stress-responsive biological system may serve as a pattern for the environmental contribution of early life stress on the diathesis for the subsequent illness (Newport, Stowe, & Nemeroff, 2002).

1.2.2 Maternal deprivation in rodents

In these models rat pups are separated from their mother for prescribed interval(s) before weaning. Maternal separation in the rat potentiated behavioral changes resembling anxiety and depression (Pryce, Bettschen, & Feldon, 2001). Furthermore, maternal separation induced acute changes in HPA axis activity, as indicated by increases in serum corticosterone and ACTH concentrations (De Kloet et al., 1988; Ladd, Owens, & Nemeroff, 1996; Plotsky & Meaney, 1993; Rasmusson & Charney, 1997). Maternally separated rat pups also exhibited neurobiological changes but it seems that the timing of the separation potentiated this effect. For instance repeated separation of 4-6 hours per day on postnatal days 6-20 induced increased ACTH responses but normal corticosterone responses to subsequent stress in adulthood (Ladd et al., 1996). Compared to a single 24-hour separation beginning on postnatal day 3 produced a normal ACTH response but an increased corticosterone response to subsequent stress. Taken in isolation, the specific significance of these findings may be unclear, but overall they demonstrate that interruption in maternal care during a period of rapid CNS development may produce lasting neurobiological alterations (Newport et al., 2002).

1.2.3 Sensitization Models

Finally, animal models have also contributed to the understanding of environmentally acquired vulnerability to disease. Stress sensitization models have been used to demonstrate that exposure to one stressor can alter the response to milder stress exposures. In a predator exposure model, rats placed briefly in a small enclosure with a cat later demonstrated increased anxiety-like behaviors that were detectable after the initial exposure (Adamec & Shallow, 1993; Pynoos, Ritzmann, Steinberg, Goenjian, & Prisecaru, 1996). Similarly, animals exposed to a foot shock and then repeatedly introduced to the setting of that initial stressor develop an exaggerated acoustic startle (Board, Persky, & Hamburg, 1956). One frequent application of animal models relevant to the diathesis-stress model has been to study the bio-behavioral sequelae of early stress. In these models young animals have been exposed to non-specific noxious stimuli such as foot shock or restraint. Pynooos et al., repeatedly re-exposed animals to a context, in which they previously received footshock, while preventing the animals from directly encountering the chamber where footshock occurred. These animals developed an increased acoustic startle reflex as well as increased aggressivity, compared to animals that where shocked, but not reposed to the shock context.

1.3 Neurodevelopmental theories of severe mental illness

Considerable heterogenity exists in the symptomatology of the major psychiatric disorders. In attempting to understand the antecedents of psychopathology, theorists historically have sought explanations from two spheres (1) on the one hand, the belief that people who develop a psychiatric disorder differ premorbidly from those who do not develop a disorder (Adler & Hillhouse, 1996) and (2) on the other hand, the belief that has long been held that stress is an important factor in the development of psychological disturbances (Kendler, Karkowski, & Prescott, 1999) Little is known about the environmental factors to the development of psychotic illnesses. Yet, it has been recognized that not all the people, even when exposed to the direst of environmental conditions, necessarily break down. Individuals, however, display a heterogeneous susceptibility to the effects of stress. Whereas some are especially resilient, others demonstrate an endogenous vulnerability toward stress-induced illness. It is this predisposition to illness, or diathesis, that provides the foundation for the diathesis-stress model (Coyne & Whiffen, 1995; Goldsmith, Gottesman, & Lemery, 1997; Monroe & Simons, 1991). During the 1960s theories of schizophrenia developed a diathesis-stress model proposing that a genetic deficit creates a predisposing vulnerability in the form of oversensitivity to stress. The diathesis-stress equation emerged when consideration was given to repositioning adverse life events as potential contributors to the diathesis (Monroe & Simons, 1991; Read et al., 2001).

Walker and DiForio (Walker & Diforio, 1997) suggested a neural diathesis-stress model for schizophrenia. In this model the authors reiterate that stress plays a pivotal role in the pathogenesis of many psychiatric illnesses and also that stressors can exacerbate symptoms but do not constitute causal factors. Their main hypothesis is that the early traumatic experiences contribution to the vulnerability of offspring to psychiatric illness may occur through numerous pathways, most notably through genetic transmission.

Regarding the neurobiology of the illness they emphasize the activation of the hypothalamic-pituitary-adrenal (HPA) axis. The classic HPA axis stress response commences with the adrenal cortex, which in turn is stimulated by the adrenocorticotropic hormone (ACTH) from the pituitary, and ultimately increased release of glycocorticoids. Equally important is also the hippocampus that contains a high density of glycocorticoid receptors (Grs) and which are expressed in this region. Another major reason that the hippocampus has been the focus of stress research is that it plays a pivotal role in the feedback system that modulates the activation of the HPA axis. It has been shown that the stress-induced increase in cortisol ultimately may be constrained through an elaborate negative feedback system involving glycorticoid and mineral corticoid receptors (Charney, 2004; Walker & Diforio, 1997). In addition to their review uncontrollable stress activates not only cortisol but also dopamine release, a neurotransmitter, consistently linked to schizophrenia. There is preclinical evidence that the susceptibility of the mesocortical dopamine system to stress activation may be closely associated with genetic determinants. Furthermore, it has been suggested that the excessive dopamine release induced by stressful events may represent a vulnerability to schizophrenia and favor helpless reactions through an inhibition of subcortical dopamine neurotransmission (Depue & Collins, 1999). Walker and DiForio go on beyond in previous reviews and nevertheless offer insights leading to the elucidation of cortisol non-suppression in the dexamethasone suppression. They document findings of higher baseline cortisol levels and a negative response to the dexamethasone suppression test, and therefore they demonstrate an association between sensitivity of schizophrenia (severity of schizophrenia symptoms) and HPA axis hyperactivity (Walker & Diforio, 1997). Further, they provide converging evidence of the role of the HPA axis on the synthesis, reuptake, and receptor sensitivity of dopamine. Dopamine is a neurotransmitter, that has been demonstrated to be involved in a number of physiological functions including HPA activation, stimulated by uncontrollable stress, which in turn elevates not only cortisol but dopamine release as well, resulting in both dopamine administration and stress producing sensitization.

1.3.1 Stress-vulnerability model

On the other hand, the stress-vulnerability model assumes that symptom severity and other characteristic impairments of severe mental illness have genetic and related biological bases (psychobiological vulnerability) determined early in life by a combination of genes and early environmental factors, such as the intrauterine environment and birth complications. Psychobiological vulnerability is determined early in life by genetic and early environmental (eg, perinatal) effects. Once the vulnerability is established, the onset of the illness and its course, including relapses, is determined by the dynamic interplay of biological and psychosocial factors, as illustrated in Figure 1.1 (Mueser & McGurk, 2004).

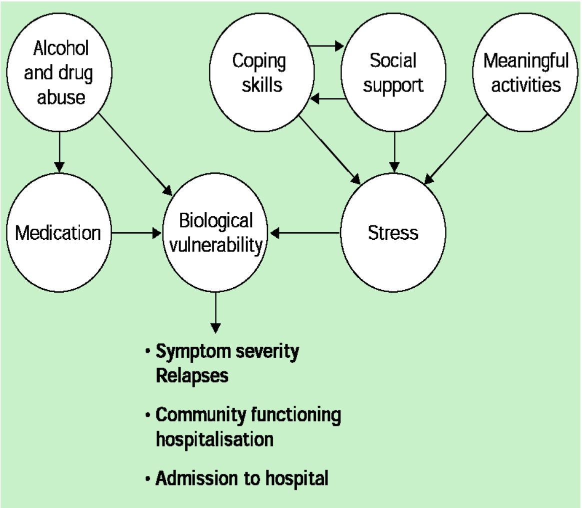

Figure 1.1: Stress vulnerability model of severe mental illness. The outcome of schizophrenia –including of symptom severity, relapses, and hospital admission- is determined by a combination of biological and psychosocial factors (adapted from Mueser & McGurk, 2002).

The vulnerability stress model in schizophrenia posits that the interaction of psychosocial stressors with a biological vulnerability for schizophrenia results in symptom exacerbations (Norman & Malla, 1993). Taken within this framework, the experience of trauma could act as a psychosocial stressor, and therefore contribute to higher levels of schizophrenia symptoms (Mueser et al., 2002). One study tested this hypothesis directly and found that individuals with a history of childhood physical or sexual abuse had significantly more positive symptoms of schizophrenia than those without a history, as well as more severe symptoms overall (Ross, Anderson, & Clark, 1994).

The assumption that the diathesis is a genetic predisposition seems to have impeded adequate consideration of the relevance of stress, traumatic events (physical or emotional), neglect, and loss by positioning all psychosocial factors exclusively in the stress component of the diathesis-stress equation. Such models differ in their details, but all assume that people have varying degrees of vulnerability to the development of schizophrenia.

Advances in the conceptualization and measurement of life stress in the past two decades raised several questions concerning traditional diathesis-stress theories of psychopathology. This growth in knowledge has been accompanied by the development of increasingly sophisticated theories that have attempted to keep pace with new findings while at same time remaining anchored in basic psychological research. Recent efforts to incorporate diathesis-stress premises in theories of PTSD appear promising. Progress towards specifying the contribution of genetic factors, psychosocial stressors, and most important, gene-environment interactions to vulnerability to schizophrenia and severe mental illness is also taking place. Most recently, theories of PTSD have explicitly adopted and extended the stress-vulnerability model developed for schizophrenia and other severe mental illnesses (Mueser et al., 2002; Read et al., 2001; Resnick, Bond, & Mueser, 2003).

1.3.2 The traumagenic neurodevelopmental model

In their article Read et al. (Read et al., 2001) take into account the alternative that for some individuals who are diagnosed with schizophrenia in adulthood, adverse life events constitute a major risk factor not only for schizophrenic symptoms, but may also, if they take place early in childhood or if they are sufficiently severe, contribute to discrete neurodevelopmental abnormalities that antedate the heightened sensitivity to stressors repeatedly observed in schizophrenic patients.

This model proposes that both genetics and psychosocial stress play a causal role in schizophrenia whereby their model is a new diathesis-stress model. According to Read et al., a comprehensive model of vulnerability to schizophrenia is needed to facilitate advances in the diagnostic accuracy, prevention and treatments (Read et al., 2001). The model must be capable of linking the neurodevelopmental effects of stress to schizophrenia vulnerability and the biochemical abnormalities repeatedly observed in schizophrenic patients (Kunugi, Nanko, & Murray, 2001; Read et al., 2001). The hypothesis that traumatic events may contribute to the vulnerability of schizophrenic symptoms is consistent with evidence revealed in a linear regression analysis, that a combination of child abuse and adult abuse predicted hallucinations, delusions and thought disorder (Read, Agar, Argyle, & Aderhold, 2003; Read & Argyle, 1999).

Despite a strong causal association between stressful life events and schizophrenia, the authors argue that part of this apparent association is non-causal, and that adverse life events are not the only determinants of susceptibility to schizophrenic symptoms. They provide a cautionary note concerning the need for caution in attribution of causality of whether adverse life events in childhood might contribute to the illness, either independently or with gene-environment interactions (Kunugi et al., 2001). Furthermore, they suggest that various methodological issues remain to be fully resolved. Understanding these issues will partly depend on studies that delineate the onset of such abnormalities within the illness course and determine whether they antedate the first overt psychotic episode.

Consequently, taken together this hypothesis leads to several predictions that may have relevance for existing views regarding the pathology of severe mental illnesses, but also for the strategic development of improved therapeutics. This model seems to be very comprehensive, but is still in testing stages. It is relatively new, and seems to have promise.

1.3.3 The interactive model of trauma

Progress has being made toward the creation of a model, which posits specific interactions between trauma exposure and the course of severe mental illness. Mueser et al (Mueser et al., 2002) proposed a model which is an extension of the stress-vulnerability model, where PTSD is hypothesized to mediate the negative effects of trauma in the course of severe mental illness. In their model Mueser et al., hypothesized that PTSD is a comorbid disorder, which mediates the relationships between traumas, increased symptom severity, and higher use of acute care services in persons with a severe mental illness. Furthermore, Mueser et al. hypothesized that each of the three symptoms clusters of PTSD influence the course of schizophrenia, ultimately resulting in more frequent relapses and higher symptom severity. According to this expanded version of the vulnerability –stress model, re-experiencing symptoms of PTSD (e.g., memories and thoughts of trauma) act as stressors, avoidance symptoms affect schizophrenia symptoms through increased social avoidance, and hyperarousal symptoms negatively influence schizophrenia through physiological pathways. Recent studies showing the high rate of early adverse life events in subjects with severe mental illness and the phenomenological overlap with PTSD have led to the hypothesis that PTSD influences psychiatric disorders both directly, through the effects of persistent PTSD symptoms on biological vulnerability and indirectly, through the effects of common correlates of PTSD such as retraumatization (Nishith, Mechanic, & Resick, 2000; Wilson, Calhoun, & Bernat, 1999), substance abuse (Back et al., 2000; Coverdale & Turbott, 2000; Gearon, Kaltman, Brown, & Bellack, 2003), and difficulties with interpersonal relationships (Gearon et al., 2003; Goodman et al., 1999; Mueser et al., 2004; Priebe, Broker, & Gunkel, 1998). Furthermore, the high rates of trauma in people with severe mental illness have also been shown to correlate with increased rates of PTSD, with most estimates ranging between 28% and 43% of patients fulfilling the criteria for current PTSD (Cascardi, Mueser, DeGiralomo, & Murrin, 1996; Craine, Henson, Colliver, & MacLean, 1988; McFarlane, Bookless, & Air, 2001; Mueser et al., 1998; Mueser et al., 2004).

PTSD is given an essential role in this model. In keeping with the assumptions of Read et al., the authors do not exclude the possibility that other important aspects might be involved in severe mental illness. As discussed elsewhere (Binder, McNiel, & Goldstone, 1996), trauma, including such early adverse life experiences, does not invariably lead to severe mental illness in adulthood.

Taken together, the theoretical accounts presented so far have converged to emphasize findings from the research literature documenting the high prevalence of psychological trauma among people diagnosed with severe mental illness. In summary the aspects of research outlined so far provide a genuine integration of biological and psychological paradigms by shedding light on the different aspects of the role of psychological trauma in severe mental illness in later live. The findings presented here indicate that adverse life events might be in some cases causally related to the development of psychotic psychopathology later in life, possibly by contributing to the diathesis in the diathesis-stress equation. However, it is argued that regardless of whether this relationship should be considered as causal contributory, co-morbid or coincidental converging evidence suggests high rates of trauma in this population, which in turn requires a broadening in trauma treatments. From this starting point it may therefore be more appropriate to consider research approaches that might clarify the relationship among environmental and genetic risk factors, to quantify the vulnerability for the development of psychiatric illness more precisely.

1.4 After all what is stress?

Stress is a nebulous term for diverse behavioral and physiological responses. The term stress is generally defined in biological systems as any condition that seriously perturbs the physiological/psychological internal state of an organism. Kim et al., have offered a three-component definition of stress that can be applied broadly across species and paradigms (Kim & Diamond, 2002). According to their definition the following issues should be addressed: first, they consider the fact that stress requires heightened excitability- arousal- which in turn can be measured via scalp recorded ERP's, behavioral activity or neurochemical responses; second, the experience must be related to avoidance as a result of aversiveness; and third, the element of control, that is the individual's ability to control the presence or intensity of the life-threatening encounters, is the variable that ultimately determines the magnitude of the stress experience (Kim & Diamond, 2002).

The body, including the brain, reacts in an adaptive physiological response to acute stress, which involves a process, initially referred to as allostasis by Sterling and Eyer. During this process the internal state milieu varies to meet perceived and anticipated demand (Charney, 2004). McEwen extended this definition to a more sophisticated and to a more conceptual one to include a set point that changes because of the process of maintaining homeostasis (McEwen, 2002; McEwen & Lasley, 2002). In contrast to homeostasis- an organism's ability to maintain a steady internal state- allostasis refers to the flexibility in adjusting to stressors (McEwen, 1998b). The responses to severe stress that promote survival in the context of a life-threatening situation may be adaptive in the short turn. However, if recovery from the acute event is not accompanied by an adequate homeostatic response to terminate the acute adaptive response of stress mediators, the deleterious effects on psychological and physiological function, termed the 'allostatic load' occur. Allostasis has evolved as the response for running away from a predator, escaping acute danger or fighting off a threat (Figure 1.2). If the allostatic load turns out to be too high -which can be defined as a state of permanent initiation of warding off stress- the psychiatric disease will be established in the form of aches, and pains, loss of appetite or overeating. A long-term allsotatic load can also have maladaptive consequences such as damaged organs, including the brain (Bremner, 1999b; Elbert & Rockstroh, 2003; Grillon, Southwick, & Charney, 1996; McEwen, 1998b; McEwen & Lasley, 2002). A psychiatric disease can be considered as a manifestation of a maladaptive brain organization that arises from unfavorable interaction of genome and environment. At its core resides abnormal cerebral network architecture with altered neural connectivity and communication. These changes can lead to neuropsychological, cognitive and behavioral malfunctioning that give rise to the psychiatric symptoms on the subjective and behavioral level (Elbert & Rockstroh, 2004). More specifically, the immediate response to life-threatening encounters is characterized by sympathetic activation which triggers the 'flight-fight-freeze' defense cascade (Elbert & Rockstroh, 2003; Grillon, Southwick et al., 1996).

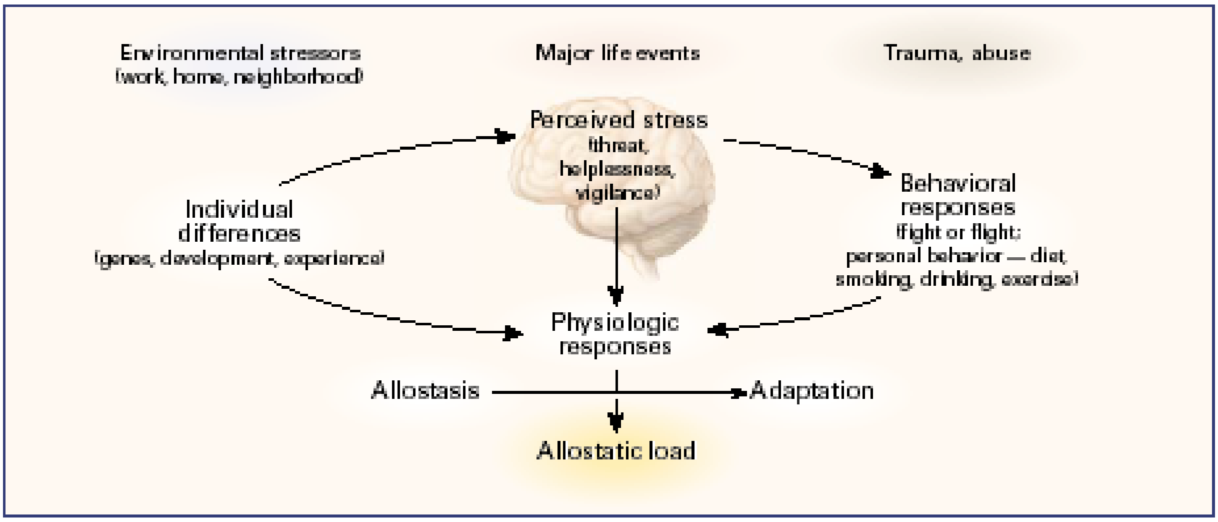

Figure 1.2: The stress response and development of allostatic load. Allostasis, the long-term effect of the physiologic response to stress. (adapted from McEwen, 1998).

The present thesis will consider allostasis and allostatic load from the perspective of the effects of extreme psychological stress on the complex regulation of emotion by the brain. Our focus in this thesis will be on mechanisms that underlie interactions between stress and emotional processing in PTSD so this should advance our understanding of how stress interferes with the ability to accurately process affective information.

1.5 Existing Knowledge about PTSD

1.5.1 Clinical Characteristics

PTSD as defined by DSM-IV is an anxiety disorder characterized by somatic and psychological symptoms that develop following exposure to catastrophic stressors. This disorder has been associated with several different types of traumatic events, including combat experience (Mollica, Wyshak, & Lavelle, 1987; Nemery, 2004; Neuner et al., 2004), torture (Basoglu et al., 1994; Mollica, 2004; Silove, Steel, McGorry, Miles, & Drobny, 2002), sexual assault (Gearon et al., 2003; Goodman et al., 1997; A. J. Lang et al., 2003; Lange et al., 1999; Nishith et al., 2000), and armed robbery (Elklit & Brink, 2004; Harrison & Kinner, 1998; Kamphuis & Emmelkamp, 1998; Verger et al., 2004).

PTSD is the only psychiatric condition that demands that a particular stressor precede its appearance. Interest in and knowledge about PTSD increased dramatically after its diagnosis was formalized in 1980. PTSD is a psychiatric condition that can develop following the experience of an overwhelmingly traumatic event (Criterion A). It is characterized by specific symptoms that develop following exposure to psychological trauma and where the person's response involved intense fear, helplessness, or horror. PTSD diagnostic criteria include intrusive re-experiencing of the traumatic event (Criterion B), avoidance of the stimuli associated with the traumatic event (Criterion C), and persistent symptoms of increased arousal (Criterion D). Of particular relevance in the psychiatric condition of PTSD are blunted emotional responses that are defined in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, American Psychiatric Association, 1994) as part of the avoidance cluster of the PTSD symptoms. In addition, the following specifiers may be used to specify onset and duration of the symptoms of PTSD: the full symptom picture must be present for at least four weeks (Criterion E). The disturbance must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning (Criterion F).

Evidence from extensive reviews of the literature suggest that the rates of PTSD, given exposure to a traumatic event, average around 25 and to 30% in the general population, although certain stressors such as rape, military combat, or natural disaster are associated with much higher rates (Green, 1994). Furthermore, converging evidence comes from longitudinal studies which indicate PTSD up to 40 years post-trauma in World War II combat veterans and in Jewish survivors of the Holocaust (Kuch & Cox, 1992).

To date, the pathophysiology of PTSD reflects long lasting changes in the biological stress response systems that underlie many of the core symptoms of PTSD. In the following sections converging evidence will be provided of the core characteristics of the neurobiological responses to stress in PTSD with an emphasis on proposed defensive and appetitive motivational systems involved in emotional perception in PTSD. Echoing the results of animal studies, alterations in affected neural systems in PTSD are reviewed, specifically the hypothalamic-pituitary-adrenal axis (HPA-axis), catecholaminergic and serotonergic systems.

1.5.2 Neurobiological responses to stress in PTSD

As early as in the 1872 Darwin (Darwin & Ekman, 1872) and Cannon (Canon, 1915) considered fear and anxiety as being associated with emotional expression, negative affect, and sympathetic nervous system discharge. According to Cannon (1915), this response to threatening situations facilitates fight or flights reactions. Sokolov (Sokolov, 1963) subsequently called this response pattern the ***defense reaction***. The defense reaction, a pivotal reflex in the human behavioral response to threat, is characterized by anxiety and increased activity of the sympathetic nervous system. The immediate response to life-threatening encounters is characterized by sympathetic activation which activates the ***'flight-fight-freeze'*** defense cascade (Figure 1.3) (Elbert & Rockstroh, 2003; Grillon, Southwick et al., 1996). However, a large body of evidence suggests that fear and stress affect multiple neurobiological systems that are fundamental for survival. More specifically, these systems are involved in identification of stimuli associated with threat or aversive situations, immediate response of motivational circuits related to confrontation (e.g., fight) or escape (e.g., flight). Moreover, these motivational circuits determine the general mobilization of the organism, the deployment of reflexive approach and withdrawal behaviors (P. J. Lang, Davis, & Ohman, 2000).

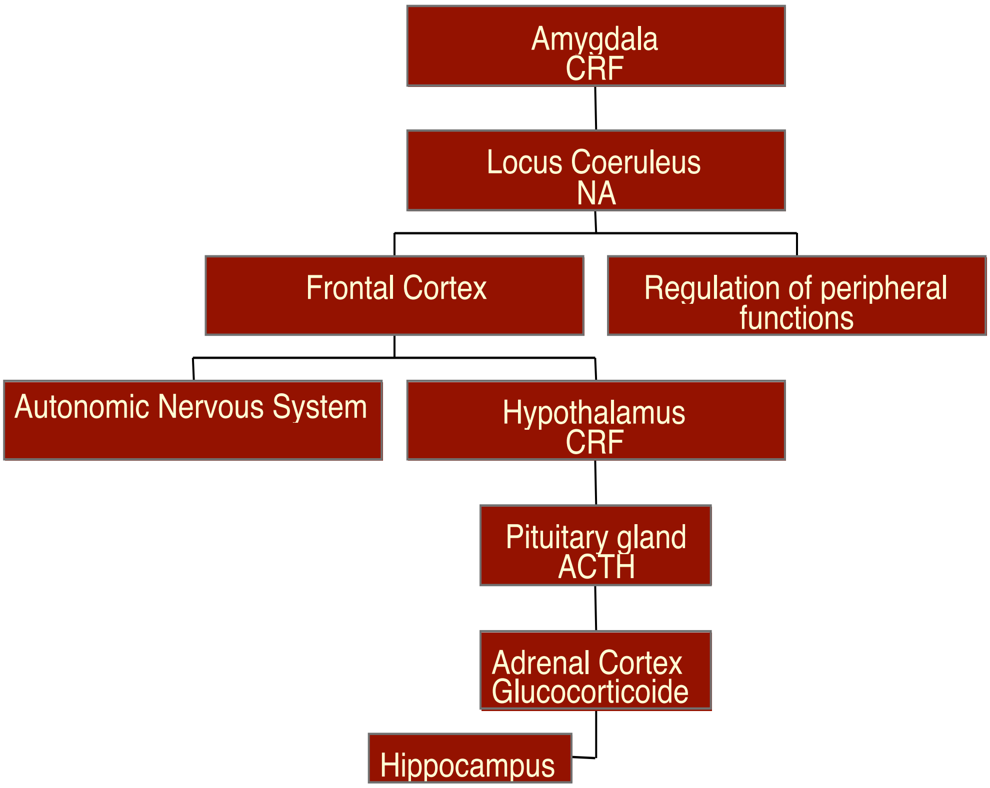

Figure 1.3: Response cascade to stressors (adapted from (Elbert, 2002)).

As a result, most evidence from animal research implies that it is possible that representations of simple lights and tones can through aversive association come to trigger neural defense circuits in animals (Greenwald, Bradley, Cuthbert, & Lang, 1998; P. J. Lang, Bradley, & Cuthbert, 1998b; P. J. Lang et al., 2000; Shors et al., 2001). Animal studies indicate that several brain structures, and multiple neurotransmitter and hormonal systems are involved in the reaction to acute trauma. Moreover, chronic behavioral stress is known to affect the structure and the circuitry of the brain, altering subsequent responses to a variety of situations (Charney, 2004; Magarinos, Verdugo, & McEwen, 1997; McEwen, 1998a; Radley et al., 2004). Animal research has illuminated these neural systems and defined their reflex outputs.

More specifically, stress activates the locus coeruleus (LC), which is the major noradrenergic (NA) system in the brain, which in turn results in increased norepinephrine

(NE) release in projection sites including the amygdala, the prefrontal cortex, and the hippocampus. Norepinephrine release has been implicated in orienting, selective attention, hyervigilance, autonomic arousal, and fear. Activation of the locus coeruleus is adaptive and protective to survival from a life-threatening situation and has been involved as a general alarm function. Furthermore, activation of the locus coeruleus also contributes to the sympathetic nervous system and the HPA axis, which is also involved during this ‘alarm response’(McEwen, 1998a; Radley et al., 2004). McEwen considers the HPA axis as essential of the defence cascade (McEwen & Lasley, 2002). Several hormones are released during this stress response. Accumulating evidence suggests that long-term changes in the HPA activity due to high allostatic load results in dysfunction of the medial prefrontal cortex and dysfunction of this structure is associated with PTSD (Pissiota et al., 2003; Rauch et al., 2003; Shin et al., 2001; Yamasue et al., 2003). Studies involving stimulation of PTSD symptoms through noradrenergic stimulation or exposure to traumatic cues resulted in a decrease in function of the media prefrontal cortex (Bremner, Narayan et al., 1999). The autonomic nervous system appears to initiate short-term corrective responses in order to maintain the organism’s internal state. Hormonal mechanisms provide a more unremitting defense against aversive events (Yehuda, 1997). A negative correlation between dehydroepiandrosterone (DHEA) reactivity- an adrenal steroid which is also released under stress- to adrenal activation has been reported, suggesting that increased levels of DHEA in response to severe stress may be protective in PTSD patients (unpublished work by Rasmusson et al).

The ability of acute stress to co-activate the HPA axis and the locus coeruleus-systems facilitates the encoding of memories for events especially for aversively charged emotional memories, beginning at the amygdala. The emotional impact is added by the amygdala and, through its connections to the frontal cortex. During acute stress the amygdala inhibits the prefrontal cortex and stimulates hypothalamic CRH release. Persistent elevation of hypothalamic and extra-hypothalamic CRH contributes mightily to the psychobiological allostatic load. Emerging evidence from functional neuroimaging, neurophysiology highlights the amygdala's central role in the appraisal of threat signals. The amygdala allocates emotional meaning to otherwise harmless stimuli and may play a pivotal role in the recollection of emotional events. Higher order sensory cortices are involved in the perceptual representation of stimuli and their constituent features. The amygdala is one structure that is anatomically positioned to participate in such perceptual processing, as it receives inputs through parallel and converging channels, each of them conveying a different aspect of the stimulus (LeDoux, 1992, 1995, 1996). The thalamus for example, conveys low-level stimulus features such as a low-level representation of the external world. At the same time these low-level features can prepare the amygdala to process more complex information resulting from sensory cortices and hippocampus. In this way, it can influence memory, attention, and other cognitive functions on the basis of the emotional meaning of the stimuli that are being processed.

The hippocampus in turn is also activated under severe stress and plays an important role in more complex aspects such as spatial memory, contextual learning and allocation of emotional significance to places and complex stimuli. Its essential role lies in forming memories, particularly those for context (Eichenbaum, Otto, & Cohen, 1992; Hartley, Maguire, Spiers, & Burgess, 2003; LeDoux, 1995; Maguire et al., 1998). Under severe traumatic stress it may be possible that the hippocampus may be affected through different chemical messengers resulting in specific cognitive deficits in spatial learning and memory. (Magarinos et al., 1997; McEwen et al., 1997). Echoing the results of animal studies, stress is associated with damage to the hippocampus (Kim & Diamond, 2002; Magarinos et al., 1997; McEwen, 1998a; Vyas, Mitra, Shankaranarayana Rao, & Chattarji, 2002). Suggested mechanisms have included elevated levels of glycorticoids (Luine, Villegas, Martinez, & McEwen, 1994) that have been reported in repeated psychosocial or restraint stress resulting in atrophy of apical dendrites in CA3 pyramidal neurons of the hippocampus (Magarinos et al., 1997).

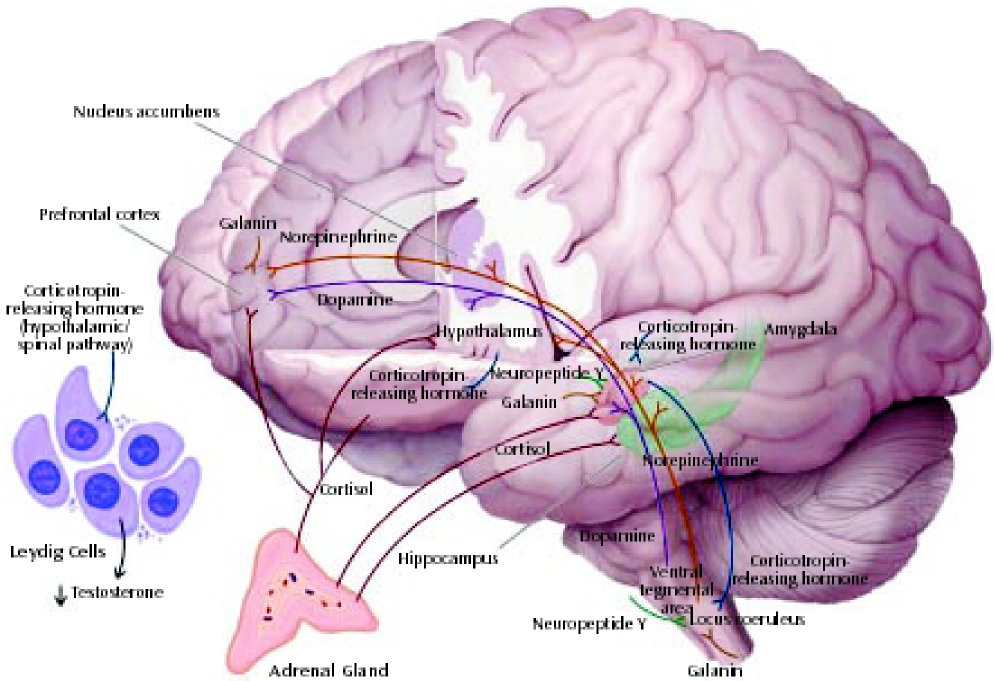

Figure 1.4: Neurobiological/-chemical response patterns to acute stress (adapted from Charney, 2004).

Persistent responses to severe stress are obviously adaptive and protective, and have survival value but they also can have maladaptive consequences if they become chronically activated (Elbert & Rockstroh, 2003, 2004). Along similar lines, glycocorticoids can have neurotoxic effects in the hippocampus that appear to affect learning and memory (Yehuda, 1997; Yehuda, Golier, Halligan, Meaney, & Bierer, 2004; Yehuda & McEwen, 2004). Persistent hyperresposiveness of the locus coeruleus-norepinephrine system may result in chronic stress-related disorders for instance anxiety, fear, and intrusive memories such as in some patients with PTSD (Geracioti et al., 2001; Southwick et al., 1997).

As such, the neurobiological responses to stress involve a conglomeration of adaptive alterations that are specific to each individual and are influenced by an individual's perception of a situation and an individual's general state of physical health, which is not only genetically-determined, but also influenced by behavioral and lifestyle choices (McEwen, 2004).

1.6 Contemporary models on emotional processes

Cognitive scientists consider mental contents, as related networks of information units. Ideas of knowledge structures have dominated the scientific understanding of features and how these are stored and interrelated. In this sense representations could be defined as permanent units of memory that are localized in neural networks that encode information and when activated, permit access to this stored information. Representational units would store elements of knowledge. Of particular interest in the present thesis is the fact that some stimuli and the associations they evoke result in a state of emotional arousal particularly in PTSD patients. However, in affective states, how differences in these systems relate to differences in the emotional experience of individuals, and which brain systems underlie emotions, and whether different regions underlie different emotions, and how emotion processing in the brain interrelates with cognition, motor behavior and motivation have been some core questions addressed by research in affective neuroscience. Around 1882, James in his seminal paper entitled ‘What is an Emotion?’ controversially proposed that emotions are no more the experience of sets of bodily changes that occur in response to emotive stimuli. Carl Lange developed similar ideas in 1885, providing us with the James-Lange theory of emotions (1890). The James-Lange theory has however remained influential since it emphasizes the embodiment of emotions, especially the arguments that changes in the bodily concomitants of emotions can alter their experienced intensity. Nevertheless, it is now widely accepted that emotions involve the integrated activity of various parts of the central and peripheral system (P. J. Lang, Bradley et al., 1998b). It remains debatable however, what gives rise to the subjective states of awareness that we call emotional experience. Considerations can be raised with regard to definition, conceptualization, operationalization of emotion. Apart from these considerations, emotion is considered as motivationally tuned states of readiness (P. J. Lang, Bradley et al., 1998b). In fact, 'emotions can be thought of as states that coordinate the homeostasis in a complex dynamic environment' (Adolphs, 2003). In recent years basic experiments from both the animal and human research laboratories have founded theoretical models of emotion. Cacioppo and Gardner (Cacioppo & Gardner, 1999) have provided with new technical instruments and methodological approaches new insights into the nature of emotional processes based on large scale functional data of the human brain (Cacioppo & Gardner, 1999). However, it is beyond the scope of the present thesis to present an exhaustive discussion on the various theoretical approaches to emotion which have been successfully reviewed by Cacioppo and Gardner 1999 (Cacioppo & Gardner, 1999). Instead I will focus on contemporary models of emotional processes relevant for the question examined here. One starting point for considering underlying mechanisms of processing of emotional information can be found in the following sections where contemporary models of emotional processes are presented in detail having important implications for the psychophysiological study of emotions in PTSD.

Proponents of cognitive theories of emotional disorders consider anxiety states as arising from the activation of cognitive structures concerned with the processing of information related to personal threat or danger (A. T. Beck, 1976; J. M. G. Williams, Watts, MacLeod, & Mathews, 1988). Information-processing theories have been developed to explain the emotional consequences of trauma. Information processing models of PSTD postulate that trauma experiences are stored in an organized schema or networks, which are likely to enhance attention and sensitivity to those stimuli perceived to be threatening or trauma related (Foa & Kozak, 1986; Foa, Steketee, & Rothbaum, 1989; Litz, Orsillo, Kaloupek, & Weathers, 2000). The importance of these models lies in cues reminiscent of the trauma that can activate a neural network of trauma-related associations that result in conditioned emotional responses and re-experiencing phenomena (Litz & Keane, 1989). PTSD is distinguished from other disorders by the unusually coherent and stable network of trauma memories that requires few matching elements before the network is activated (Foa et al., 1989). Consistent with this view, Foa et al., (Foa & Kozak, 1986; Foa et al., 1989) have suggested that the symptoms of PTSD are most probably conceptualized in terms of Lang`s fear network (P. J. Lang, 1979). A number of psychological paradigms provide frameworks for understanding PTSD. These argue that presentation of information represented in such a fear structure activates it and finally evokes a fear response and triggers strategies to escape or avoid fearful stimuli (Foa & Kozak, 1986; Foa et al., 1989).

In the present thesis the fear network will be investigated through converging measures. The theoretical accounts of Lang and coworkers will be discussed below in detail, because the present thesis adopts some important positions of Lang's views on the relationship between emotion and attention, as well as the motivational characteristics of affective valence and arousal.

1.6.1 The LeDoux model

Substantial insights into the nature of the brain mechanisms involved in emotion have come from the work by Joseph LeDoux on fear conditioning in nonhuman mammalian species. The model proposed by LeDoux and his coworkers is based on work on the fear-potentiated startle reflex in rodents (LeDoux, 1995). In fear conditioning, meaning less stimuli come to obtain fear-inducing properties when they occur in conjunction with a naturally threatening event such an electric shock. As a result, converging evidence from rodents indicated that if a rat hears a tone followed by a shock, after a few such pairings the rat will respond fearfully to the tone, exhibiting a potentiated startle response. This fear-potentiated startle response is accompanied by widespread activation in rodents in autonomic (heart rate and blood pressure), in endocrine and motor (freezing) behavior, along with changes in hormonal systems such as analgesia, and somatic reflexes such as a potentiated startle response (Armony & LeDoux, 1997). A cumulative body of research has provided evidence for the role of two afferent routes involving the amygdala that can mediate such conditioning (Fanselow, 1994; LeDoux, 1995). The pathways involve transmission of sensory information from processing areas in the thalamus (Ledoux & Muller, 1997). According to LeDeux's model the lateral nucleus (LA) is the sensory input region of the amygdala as has been shown by anatomical, behavioral and physiological studies (Bordi & LeDoux, 1992; LeDoux, Cicchetti, Xagoraris, & Romanski, 1990; LeDoux, Farb, & Ruggiero, 1990; Romanski & LeDoux, 1992). Specifically, when sensory information is processed, the first route reflects a direct thalamo-amygdala route that processes sensory aspects of incoming sensory stimuli and that immediately relay this information to the amygdala. In the case where one of these incoming stimuli represents signals of threat, then an early conditioned fear response can be observed. The second route is a thalamo-cortico-amygdala pathway that permits more complex analysis of the incoming sensory stimulus and delivers a slower, conditioned emotional response. Although most of the findings were obtained from studies with experimental animals, some evidence is emerging suggesting that analogous brain regions and mechanisms are involved in human fear conditioning.

Converging evidence comes from recent studies in patients suffering from selective amygdala lesions, which exhibited marked deficits on the acquisition of autonomic conditioned responses during a fear-conditiong paradigm(Aggleton, 1993). In addition, one study by Angrilli and colleagues, described a patient with extensive right amygdala damage who exhibited a reduced fear startle potentiation to a sudden burst of white noise (Angrilli et al., 1996). Similarly, in another study a patient with bilateral amygdala damage exhibited the same response pattern as described previously, namely failure to fear conditioning to aversive stimuli. Nevertheless this patient was aware of the experimental reinforcement contingencies (Bechara et al., 1995). In contrast, evidence of normal conditioned fear response was found in a patient with an intact amygdala, but with hippocampal damage. These investigators concluded that this patient had no explicit memory about the conditioning procedure, although he acquired normally the conditioned fear response (Bechara et al., 1995). Furthermore, evidence comes from imaging studies where Morris and colleagues showed that the amygdala was activated differentially in response to fear-conditioned angry faces that had been previously paired with an aversive noise, compared with angry faces that had not been paired with noise (Morris, Ohman, & Dolan, 1998). In line with LeDoux's ideas, convergent evidence suggests that masked presentations of conditioned angry face operates through thalamo-amygdaloid connections (Morris, Ohman, & Dolan, 1999).

In addition, some findings indicate that the amygdala is also involved in processing of emotional facial expressions (Adolphs, Tranel, Damasio, & Damasio, 1994; Young et al., 1995). This involvement of the amygdala in the processing of facial expression has been supported by neuroimaging studies. For example, Morris and colleagues using PET (Morris et al., 1996), and Breiter and colleagues using fMRI (Breiter et al., 1996) , showed selective brain activation in the amygdala in response to the presentation of fearful faces. The activation of the amygdala was also present even when faces where presented in a subliminal backward masking procedure so that the subjects are unaware of them (Morris, Ohman et al., 1998; Whalen, Rauch et al., 1998), or emotional facial expressions are presented in the blind (right) hemifield of patients despite an extensive lesion of the corresponding (left) striate cortex (Morris, DeGelder, Weiskrantz, & Dolan, 2001). The investigators conclude that a colliculo-thalamo-amygdala neural pathway could process fear-related stimuli independently of both the striate cortex and normal visual awareness. Taken together, these data emphasize the importance of the direct thalamo-amygdala pathway in the human brain and support the amygdala's implication in the non-conscious monitoring of emotional stimuli. Finally, as well as its role in fear conditioning, the amygdala has also been involved in appetitive conditioning (Gallagher, Graham, & Holland, 1990). Furthermore, in one study responses detected by fMRI reported activation of the amygdala during viewing of erotic arousing material (Karama et al., 2002). Taken together, these results indicate the amygdala plays a crucial role also in the elaboration of positive or pleasant stimuli that have particularly arousing or motivating features.

The idea that afferents converge on the lateral nucleus of the amygdala which projects the basal and accessory basal nuclei which in turn projects to the central nucleus influencing various systems that are mediators for a number of brain/behavioral functions according to stimulus significance. LeDoux views emotional evaluation, expression, and experience as having separate brain substrates and so propose separate empirical approaches for investigating these constructs. As a result, emotional evaluation is considered as a sub-conscious mechanism whereas emotional expression or experiences are viewed as conscious states. In this sense the amygdala is thought to mediate unconscious low-level pivotal affective processes that are triggered automatically and prepare the organism for certain behavior tendencies (e.g. fight/flight).

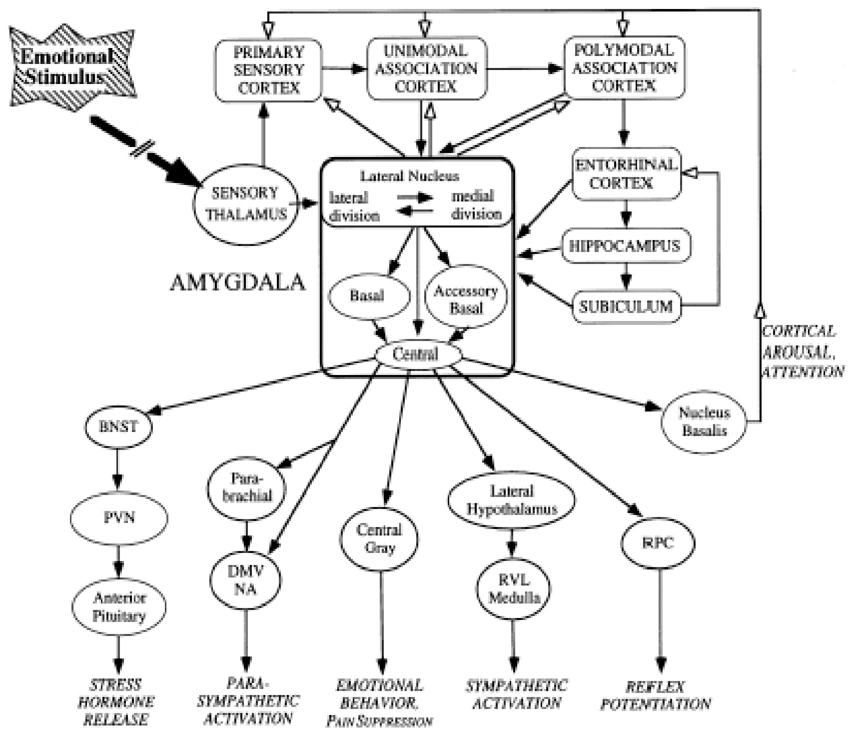

Figure 1.5: Fear conditioning pathways involving the amygdala, according to the LeDoux model (adapted from LeDoux, 1997; see text for details). A hierarchical cascade of auditory information converges onto the lateral nucleus of the amygdala. After processing in the amygdala the information reaches the central nucleus.

1.6.2 Damasio's model on emotion - Somatic marker hypothesis

One of the most influential approaches of human emotions in the field of functional neuroanatomy of emotion has been developed by Damasio and coworkers (Damasio, Grabowski, Frank, Galaburda, & Damasio, 1994). The somatic marker hypothesis builds on earlier work of Nauta (Nauta, 1971) who used the term 'interoceptive' markers rather than somatic markers, and Pribram (Pribram, 1970) who used the phrase 'feelings as monitors', and reflects the original ideas of the James-Lange theory. That is, bodily signals interact with other forms of cognition to generate emotional experience, rather than existing as the single determining factor. Consistent with this viewpoint, Damasio and coworkers continued in similar patterns involving again the key role for bodily feedback in emotion, implicating the prefrontal cortex (PFC), especially the ventromedial PFC. Two important aspects of Damasio's theory are the categorization of 'emotion' in terms of 'primary' and 'secondary' emotions and the clear distinction from the expression 'feeling'. In this sense, emotions are defined as *'the combination of a mental evaluative process, simple or complex, with dispositional responses to that process, mostly toward the body proper, resulting in an emotional body state, but also toward the brain itself (neurotransmitter nuclei in brain stem), resulting in additional mental changes'* (Damasio et al., 1994). Basically, somatic markers are physiological reactions, such as shifts in autonomous nervous system activity, which tag previous emotionally significant events. Damasio has argued that somatic markers are stored memories of somatic states that are associated with current events- particular behavioral experiences or outcomes. An important aspect of this model is the linkage of somatic markers with behavioral experience. A pivotal role is attributed in Damasio's model to the PFC, especially the ventromedial PFC. The ventromedial PFC is described as a 'convergence zone' in which information from both sensory cortices and limbic structures, mainly the amygdala and the anterior cingulate (AC) interacts to regulate behavior according to previous experience (Damasio et al., 1994). The somatic marker hypothesis predicts that damage to the ventromedial PFC will result in an impaired ability to use somatic markers, and for that reason, in poor decision-making. In this sense, the somatic markers enable the individuals to navigate themselves through situations of uncertainty where decisions need to be made on the basis of the emotional states of the present environmental context. In addition, the somatic marker hypothesis predicts that emotionally charged stimuli should be associated with activation of ventromedial PFC and with somatic responses (chances in electrodermal activity or heart rate). Several sources of evidence are consistent with these predictions such as studies from electrophysiology (Bechara, Damasio, Tranel, & Damasio, 1997; Kawasaki et al., 2001; Zahn, Grafman, & Tranel, 1999), and from human lesion studies (Anderson, Bechara, Damasio, Tranel, & Damasio, 1999; Bechara, Tranel, & Damasio, 2000; Bechara, Tranel, Damasio, & Damasio, 1996). The somatic marker hypothesis would benefit from expansion that is to take into account the functions of the PFC regions in processing social stimuli and as well as how this processing influences the ventromedial PFC.

1.6.3 The Lang model

How are emotions embodied in the brain? Which brain systems underlie emotions? These are some of the core questions of Lang's theoretical model of emotion that proposes that there are two basic motive systems that organizing the response systems in emotion. These two motivational systems are organized as being either consummatory/appetitive propensities or defensive/aversive propensities. In this sense, human emotions can be viewed as action dispositions, which result in pivotal physiological changes mediated by the somatic and autonomic systems. As a result, this approach of Lang and his associates is related to a two-dimensional (2D) model of emotion: the **affective valence dimension** and **arousal dimension**. The valence refers to the direction of behavioral activation associated with emotion, either toward (appetitive motivation, pleasant emotion) or away from (aversive motivation, unpleasant emotion) a stimulus. Arousal is proposed to be orthogonal to valence and refers to the intensity of emotional activation, ranging from excited to calm. The valence dimension is related to variations on the level of the two motive systems, i.e. 'appetitive' versus 'aversive' and this is connected to an action disposition organizing behavior along avoidance –approach dimension. The arousal dimension adds to the 2D affective space a component that modulates the emotional behavior regarding activation or intensity (P. J. Lang, Bradley, & Cuthbert, 1998a). Thus, at the level of human emotion, correlations between the affective state of the organism and the behavioral outcome are quite modest and can vary considerably within subjects and in terms of different behavioral contexts. In this sense, the motivational system determines the organism's state either through external threat or either internal associations involving '*strategic'* responding (defense or appetitive acquisition) versus *'tactical'* responding. Though the '*strategic'* response patterns are associated with the disposition of a given organism to respond, to defend, the *'tactical'* response patterns form the somatic and the autonomic demands of the respective situation. Affective responding is in great part a *'tactical'* response to contextual demands (P. J. Lang, 1994).

The two motivational circuits namely the appetitive/defensive, with regard to the dimension of affective valence, it is postulated that these motivational systems exist in the brain and that each can vary considerably in intensity of activation. That is, they may involve neural networks underlying emotion including direct connections to neocortical and subcortical structures. The dimension of affective arousal it is thought not to be involved in a separate structure, but rather reflecting changes in terms of activation, either for the aversive or the appetitive subsystems or the co-activation of both systems (P. J. Lang, Bradley et al., 1998b).

As a hypothetical construct of the response systems underlying emotion, Lang and coworkers have also addressed the question how emotions are mentally represented and proposed that emotions can be viewed as a *propositional network*, which can be analyzed into propositions. Accordingly, human emotions are considered as represented by information structures in memory and are activated when any component stimulus is encountered (P. J. Lang, 1994; P. J. Lang & Cuthbert, 1984). The elements of such a structure are viewed as *cognitive representations* of the stimulus characteristic of the fear situation, the individual responses to it, and aspects of its meaning for the individual. An example of such a hypothesized fear network can be seen in Figure 1.6. Fear networks are stored in memory and consist of three pivotal elements, (i) *stimulus propositions* containing information critical to recognition of the external stimulus and to the context in which it occurs, (ii) *response propositions* containing information concerning the person responses to the fear stimuli such as physiological (i.e., visceral and somatic indices of physiological arousal) and behavioral (i.e., verbal statements, overt act), and (iii) *meaning propositions* containing information on stimulus/behavior contingencies that define the individuals interpretation of the fear-related stimuli. This information structure is thought to be as a mechanism for escape or avoidance. In this sense, Lang and coworkers in trying to account for physiological responses measured during fear proposed that fear is accompanied by widespread physiological activity. A measurable feature of this fear state has been tested extensively using the so-called 'startle response paradigm' (P. J. Lang, Bradley, & Cuthbert, 1990). More specifically, an example of what a 'startle response paradigm' is called is, when the subject is looking at standardized affective pictures, which allow for a manipulation of the valence and intensity of affective pre-activation. Startle probes consist of either a burst of white noise or a sudden flash of light. The kind of the startle probe we applied in our experimental design and how the eyeblink component of the startle response was assessed is discussed in the Study II (see methods section). Interpretation of the startle probe modulation by a pictorial foreground in humans has been repeatedly investigated from a great number of authors: It is thought that the startle reflex is enhanced or inhibited, depending on whether the affective valence of the foreground and the probe match or mismatch. Furthermore, there is evidence pleasant picture viewing may be assumed to promote startle inhibition, whereas aversive picture viewing promote startle facilitation (Bradley, Cuthbert, & Lang, 1990; P. J. Lang et al., 1990; Vrana, Spence, & Lang, 1988). Results from these studies provide further support for the 'emotional priming model' by demonstrating that the congruence between in an aversive affective state and the aversive tone results in an enhancement of the startle reflex, whereas the incongruence between being in an appetitive affective state and the aversive stimulus results in startle probe inhibition.

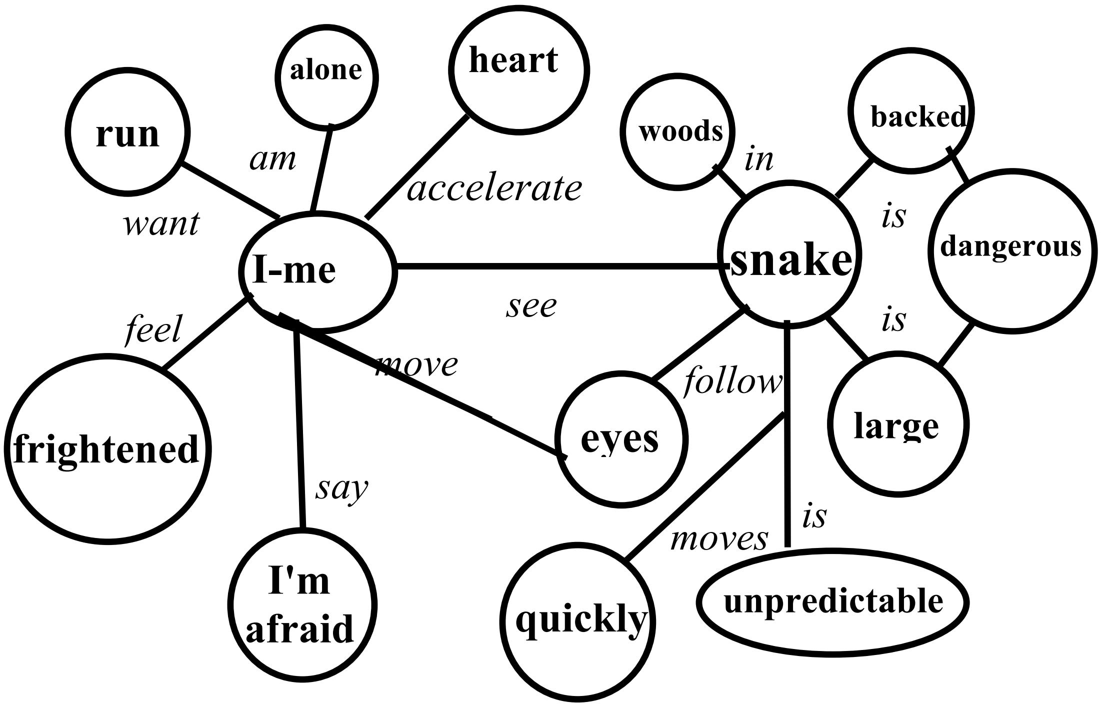

Figure 1.6: Propositional network modeling a snake phobia (adapted from Lang, 1994)

Given the essential role of the affective stimuli in this paradigm, Lang and co-workers have developed the International Picture System (IAPS) (P. J. Lang, Bradley, M.M., Cuthbert, B.N., 1999), a collection of calibrated photographic slides which has normative ratings of valence, arousal and dominance. As well as the International Affective Digitized Sounds (IADS), a similar collection of acoustic stimuli has been developed. In addition, a subjective rating instrument (Self-Assessment Manikin, SAM) has been developed (Bradley & Lang, 1994), which allows for assessing the self-reported emotional experience of participants in a given experimental setting. The present investigation assessed the IAPS and the self-assessment scale details are discussed in the Study B (for further information, see Methods section).

In the last decades the assessment of clinical anxiety has been influenced by Lang's proposal that anxiety involves three systems namely physiological activity, subjective report, and overt behavior (P. J. Lang, 1968, 1979). Furthermore, Lang and coworkers have attempted by integrating elements from clinical psychology, neuroscience, cognitive psychology and psychophysiology to understand of the manner in which emotional processes are represented in the brain. Thus, the Lang model has a strong focus on the emotional processes that are identified to involve networks sensitive for visual stimulation. Taken together, the conception on Lang's model presented so far can provide substantial insights into the linkage between the proposed network and PTSD. For example, Pitman and Orr have hypothesized that PTSD may be conceptualized as consisting of one or more pathological emotional networks, which when activated can trigger its characteristic re-experiencing symptomatology (Pitman & Orr, 1990; Pitman, Orr, Forgue, de Jong, & Claiborn, 1987). Lang's proposal that emotions are represented in networks has essential clinical implications, in particular when discussing the cognitive basis and treatment of anxiety disorders (P. J. Lang et al., 2000).

In terms of specific approaches outlined so far each of them endeavors to explain only a circumscribed set of empirical and clinical findings, depending on database, methodology or theoretical or professional background of the author. Furthermore, although all the models are supported to some extent by the available cognitive neuroscience data, it is not the case that each model addresses all of the available data. Finally, there is a variability in the degree to which these models are guided by psychological learning theory either as a framework on the behavioral level such as the Lang model or rather as an experimental technique as in the

LeDeux model. In this sense the accounts we have offered provide a theoretical framework to explain emotional processing and the mechanisms underlying it. However, we propose that is necessarily to provide a useful development to define emotion on a variety of levels, including behavioral, neural and cognitive level, as was suggested by Gray. These levels must be associated to a semantic framework by the motivational or the learning aspect of the stimuli that could account for it. In the following sections we will highlight the importance of understanding how emotional stimuli are processed and how the underlying motivational structure is apparent in the organization of behavioral, visceral and cortical responses, the later based on converging evidence from recent advances in functional neuroimaging and of scalp recorded event-related potentials (ERPs).

1.7 Processing of affective visual stimuli: empirical findings- evidence from neuroimaging findings

Neuroimaging techniques such as positron emission tomography (PET) and functional Magnet Resonance Imaging (fMRI) have been used to map brain regions associated with the visual processing of emotional stimuli in human subjects. Especially, functional neuroimaging has been another valuable tool in identifying the neural sources since the BOLD response reflects changes in blood oxygenation that occur several seconds after the corresponding events. However, by keeping this in mind, several sources of evidence have implicated several regions of the human brain that are specifically activated when visual input is processed. It seems that the brain regions that have been implicated in affective picture processing have lead some researchers to suggest that these regions represent a distributed network for visual-emotional associations. This network includes areas in the bilateral amygdala, the anterior cingulate, several areas in the prefrontal cortex, and the visual cortices. One limitation of these studies is that they show little convergence with respect to regions suggested to be involved in affective perception. In addition, there is controversy surrounding lateralization of emotional systems in general or lateralization consistent with the content or valence of emotions (R. J. Davidson & Irwin, 1999; Lane, Reiman et al., 1997; Liotti & Tucker, 1995).

With these caveats in mind, results from an fMRI study during emotional IAPS picture processing showed that emotionally arousing pictures were associated with enhanced BOLD responses in visual cortex, as compared to calm pictures. Using PET, Lane et al., examined regions of brain activity in a group of female subjects during picture viewing from the IAPS. Emotional pictures elicited BOLD responses in the left parahippocampal gyrus, the hippocampus and amygdala. More precisely, cortical structures involved were the left and right occipital gyrus, the right fusiform gyrus and the right inferior and superior parietal lobules (Lane, Reiman et al., 1997). In a study designed to investigate emotion-specific activation in visual cortex, fMRI revealed that functional activity was greater in occipital than in occipitoparietal regions when processing emotional pictures (pleasant or unpleasant) than when processing neutral pictures (P. J. Lang, Bradley, Fitzsimmons et al., 1998). In addition, results from several imaging studies indicate that emotional content modulates brain activation in the visual cortex (H. Critchley et al., 2000; Lane, Chua, & Dolan, 1999; Taylor, Liberzon, & Koeppe, 2000; Vuilleumier, Armony, Driver, & Dolan, 2001). Furthermore, structures outside of the limbic system also are activated during emotional processing of pictures and these responses are independent of the complexity of the images. Viewing affective pictures from the IAPS modulated occipital and occipital-temporal cortex activity as compared to viewing non-aversive images (Taylor, Phan, Decker, & Liberzon, 2003). In addition, results from another recent fMRI study provided further support for the amygdala involvement by using threatening and fearful non-face stimuli from the IAPS (Hariri, Mattay, Tessitore, Fera, & Weinberger, 2003). In each of these fMRI studies, a train of IAPS pictures was presented, and brain responses were examined in response to those stimuli.

Furthermore, MEG technology is only now being used as a means for examining affective processing in humans. To date, a few studies have been published examining emotional modulation of event-related magnetic fields. Evidence from a recent MEG study where high (pleasant and unpleasant) and low (neural) arousing emotional pictures were presented (Moratti, Keil, & Stolarova, 2004) has indicated that high arousing pictures (pleasant or unpleasant) elicited greater activity in frontoparietal cortical networks than low-arousing neutral pictures. Activation in the occipitotemporal regions showed a similar pattern but to a lesser extent than frontoparietal cortical regions, indicating that activity in higher-order frontoparietal cortical networks is modulated by emotional arousal. In addition, in another study Streit et al. (Streit et al., 1999) by means of a 148-channel whole head MEG system obtained MEG correlates of the recognition of facial expressions in four healthy volunteers. Subjects had to perform a facial emotion recognition task and a control task involving recognition of complex objects including faces. Results revealed that facial emotion recognition activated inferior frontal cortex, amygdala and different parts of temporal cortex in a relatively consistent time sequence. However, as to whether or not amygdala activation can be assessed using MEG remains under debate (George et al., 1995).

In summary, the results reviewed earlier based on a convergence of findings indicate that the regions recruited during the processing of emotionally pictures involve additional areas in emotion elaboration. Therefore, since visual processing of emotional stimuli is a highly relevant issue in the present thesis particularly in PTSD, in the three following sections I will provide further empirical evidence from visual evoked potentials and later I will briefly present recent findings from neuroimaging studies in PTSD and schizophrenia since this part will be discussed in detail in Study II and Study III (Methods section).

1.7.1 Processing of affective visual stimuli: Evidence from studies of visual evoked potentials

Substantial insights into the nature of affective picture processing have come from studies of scalp recorded ERP's in humans. An ERP associated with the effects of visual stimuli differing in affective valence and arousal – an enhanced P300 deflection- was described by a great number of investigators (Cuthbert, Schupp, Bradley, Birbaumer, & Lang, 2000; Keil et al., 2002; Keil et al., 2003; Keil et al., 2001; Patrick, Cuthbert, & Lang, 1994; Schupp et al., 2000; Schupp, Junghofer, Weike, & Hamm, 2003; Schupp, Ohman et al., 2004). This enhanced P300 has been interpreted as representing the engagement of neural structures in appetitive or defensive motivational systems that are responsible for a greater allocation of attentional resources for motivationally relevant and arousing stimuli (P. J. Lang, Bradley et al., 1998b). Furthermore, investigating ERP'S related to pictures, although the P300 is typically elicited experimentally by pictures taken from the IAPS it has been reported that similar potential can be derived with other stimuli material, provided that they are different in arousal from control stimuli (Carretie, Iglesias, & Garcia, 1997; Laurian, Bader, Lanares, & Oros, 1991).

Meanwhile, the potential that is most directly linked with affective picture processing is not only characterized by an enhanced P300 but also by a late positivity beginning in the time range of about 300 ms. Response to emotional pictures elicits a sustained scalp-recorded potential that peaks at about 400-700 ms after stimulus onset and reaches its maximum at around 1s (Diedrich, Nauman, Maier, & Becker, 1997; Palomba, Angrilli, & Mini, 1997). Cuthbert et al, (Cuthbert et al., 2000) showed that greater positivity for high arousing pictures (pleasant and unpleasant) compared to neutral ones was sustained even until the fifth second of picture processing. This late differentiation of this potential between emotionally arousing and calm pictures has been observed during longer presentation periods such as the 6s paradigm (Cuthbert et al., 2000) as well as in pictures that are presented with a shorter duration period (Schupp et al., 2000). Accordingly, the investigators reported that this late positivity was most pronounced during presentation of affectively arousing pictures, compared with neutral or clam IAPS slides. This again suggests, that emotional inputs undergo more processing than nonaffective stimuli and are engaged by neural structures in sustained attentive processing as reflected by the slow potential component. In addition, Diedrich et al, found that this late positivity wave was largest over frontal sites whereas the P300 component was largest at parietal sites. Furthermore, there was a discord with regard to the time course. Actually, the centro-parietal P300 decreased shortly after peaking at 300 ms after the stimulus onset whereas the frontal slow wave started only about 450 ms after stimulus onset. Accordingly, differences in frontal positivity might reflect a prerequisite for motor inhibition whereas the late frontal positivity might reflect inhibition of emotional behavior due to the experimental environment (Diedrich et al., 1997). In contrast, Schupp et al, and Cuthbert et al, reported that the P300 and the subsequent positive slow wave were largest over frontal to parietal sites. One study did found evidence by using source localization and high-density EEG that slow potential modulation is generated by higher order visual cortices (Junghofer et al., 1999). Nonetheless, because of the very small number of studies that have so far investigated slow potentials in response to affective pictures, the review outlined so far remains open.

With these caveats in mind, results from a few ERP have showed that higher order visual cortices generate the discrimination between emotional and neutral pictures. Keil at al, showed a voltage enhancement in the N1 time window for arousing compared to neutral IAPS slides (Keil et al., 2001) . In another study Keil et al., reported a sustained early negative shift for pleasant pictures over parietal and posterior electrode sides (Keil et al., 2002). Recent findings from two ERP studies using source localization and high density EEG arrays and presenting pictures with high speed presentation found the same pattern with regard high arousing pictures as compared to neutral pictures beginning at around 150 ms after picture onset (Junghofer, Bradley, Elbert, & Lan, 2001; Schupp, Junghofer, Weike, & Hamm, 2004). Source analysis in the first study by Junghoefer et al., revealed that the main sources for this early discrimination were generated by primary and secondary visual cortices (Junghofer et al., 2001). The maximum difference peaked at about 260 ms over primary and secondary visual cortices. Taken together, the results reviewed earlier raise the question whether this early discrimination between emotional salient and neutral pictures takes place before one becomes aware of it.

With regard to lateralization, there is not enough evidence to draw conclusions although a few studies have reported more reactivity to emotionally arousing stimuli over the right hemisphere (Junghofer et al., 2001; Keil et al., 2002; Keil et al., 2001) suggesting that this might reflect a stronger involvement of the right hemisphere in affective picture processing. In addition, Kayser et al found evidence for ERP asymmetries to emotional stimuli in a visual half-field paradigm. However, asymmetries in emotional processing were restricted to N2 and early P3, with maximal effects over the right parietal region. N2-P3 amplitude was augmented for negative and reduced for neutral stimuli over right hemisphere regions (Kayser et al., 1997).

1.7.2 Emotion Information Processing in PTSD: Evidence from empirical findings

1.7.2.1 Evidence from studies of visual evoked potentials in PTSD

Impairment of affective perception, experience and expression in PTSD has recently become the focus for a great deal of empirical and theoretical work. The fact that PTSD provides perhaps the best example of an anxiety disorder which appears to follow the classical fear conditioning model, in that the pathological symptoms manifest follow exposure to a traumatic event. To date, only a few studies have been published examining physiological parameters in PTSD patients during emotional picture viewing. In one study, Stanford and coworkers (Stanford, Vasterling, Mathias, Constans, & Houston, 2001) examined the ERP responses to trauma-relevant stimuli in an oddball paradigm (trauma-relevant threat, trauma irrelevant threat) in ten Vietnam War veterans diagnosed with PTSD compared to ten Vietnam War veterans with no mental disorder diagnosis. Vietnam War veterans diagnosed with PTSD showed attenuated P3 responses to neutral target items at selected electrode sites and enhanced responsivity to trauma relevant combat-stimuli at frontal electrode sites. The authors attributed these findings to an attentional bias toward threatening stimuli at the cost of attention to emotionally neutral pictures in PTSD. In another ERP study, Attias and coworkers presented pictorial stimuli such as domestic animal pictures (targets), emotionally neutral pictures of furnishings (nontargets), and combat-related pictures (nontarget probes), in an oddball paradigm. Visual evoked potentials of primary interest were N1, N2, P2 and P3. Subjects (20 PTSD patients and 20 healthy controls) were asked to discriminate between target and non-target stimuli by pressing a button in response to target stimuli only. Results demonstrated enhanced P3 amplitude over midline sites for combat probes in PTSD patients only (Attias, Bleich, Furman, & Zinger, 1996). An effect of no-target stimuli on ERP components N1, and P3 was observed only in PTSD patients. N2 amplitudes were accentuated in PTSD patients for both targets and combat-related pictures. P3 latencies and reaction times to target stimuli were prolonged in PTSD patients. The same tendency was observed for N1 latencies. These authors have interpreted their findings as supportive of an attentional bias in early and late processing in PTSD. In a subsequent study, the same author (Attias, Bleich, & Gilat, 1996) reported that P3 component in response to combat stimuli correctly classified 90% of PTSD patients and 85% of controls. However, Standford et al. (Stanford et al., 2001), has criticized these results due to methodological problems of the study designs used by Attias et al. suggesting that Attias and coworkers did not use neutral control conditions to control for unspecific effects of the experimental situations per se. In addition, the measurement of the P3 was somewhat unconventional (difference between the P3 peak and the following negativity) and limiting interpretation of the results in comparison to other ERP studies in PTSD (Stanford et al., 2001). Reviewing the literature, further evidence comes from another ERP study where Blomhoff and coworkers investigated ERP responses to emotional words in PTSD patients (Blomhoff, Reinvang, & Malt, 1998). They found that enhanced P3 component response to emotional words was associated with avoidance and arousal symptoms, although they did not find any distinction between positive and negative words. Kounios and coworkers (Kounios et al., 1997) presented rare target food words among a series of frequent neutral words and frequent trauma words. The investigators reported enhanced activity for the 250-350 ms time window in both types of frequent words, including trauma words in PTSD patients. In contrast, combat comparison subjects showed a distinct negativity. These studies seem to indicate that PTSD patients may demonstrate biases in attentional allocation toward novel or trauma-relevant material

Moreover, most evidence comes from ERP studies that have used an experimental design to elicit responses to neutral stimuli (e.g., auditory tones) revealing abnormalities on both measures of early processing (mismatch negativity, P50) suggestive of PTSD-related deficits in sensory gating (Morgan & Grillon, 1999; Neylan et al., 1999) and abnormalities of later measures (e.g., P2, P3) suggesting cognitive processing (Charles et al., 1995; Lewine et al., 2002; McFarlane, Weber, & Clark, 1993; McPherson, Newton, Ackerman, Oglesby, & Dykman, 1997; Paige, Reid, Allen, & Newton, 1990).

In summary, with some notable exceptions, there has been little attempt to understand physiological parameters in PTSD patients during emotional picture viewing. ERP studies in recent years have contributed to provide a more coherent and detailed picture of the mechanisms that are involved in emotional processing in PTSD. Although there is considerable consistence across studies as to the time course of the effect, some of the controversies that surround these ERP studies in PTSD are a limited number of electrodes and the lack of source estimation techniques. In the present thesis a 148-channel whole head magnetometer (MEG) was used as well as a source localization procedure (minimum norm estimate, MNE; (Hamalainen & Ilmoniemi, 1984).

1.7.2.2 Evidence from neuroimaging studies in PTSD

Evidence into the effects of visual stimuli differing in affective valence and arousal in PTSD is limited since the wealth of research involves either exposure of PTSD patients to traumatic scripts or symptom provocation and cognitive activation experimental paradigms. Neuroimaging studies in PTSD have demonstrated that exposure to traumatic scripts resulted in (a) increased blood flow in limbic regions such as right amygdala, insula, orbitofrontal cortex, and anterior cingulate, and in (b) decreased blood flow in middle temporal and left inferior temporal cortex by utilizing positron emission tomography (PET; (Rauch et al., 1996)). This study did not involve a control group, however, so it is not possible to determine whether changes are PTSD-specific. Evidence from another recent PET study during mental imagery in PTSD suggested that increased blood flow was implicated with activation in right amygdala and anterior cingulate, whereas decreased blood flow was implicated with activation in middle temporal and left inferior frontal cortex (Shin et al., 2001). Furthermore, symptom-provocation and cognitive activation studies using functioning neuroimaging provide further support for greater activation of the amygdala, anterior paralimbic structures, Broca's region and other neocortical regions and reduced activation of anterior cingulated cortex (ACC) in response to trauma-related stimuli in individuals with PTSD (Pitman, Shin, & Rauch, 2001; Shin et al., 2001; Villarreal & King, 2001). In one study, regional cerebral blood flow responses to trauma-related stimuli were examined in subjects with PTSD. Subjects were studied twice, while listening to combat sounds or white noise. Significant increases in the blood flow to the medial prefrontal cortex were observed in PTSD patients, but not in the control groups (matched combat exposed subjects without PTSD and healthy control subjects; (Zubieta et al., 1999). A few studies reported increased response in the prefrontal cortex (Bremner, Narayan et al., 1999; Zubieta et al., 1999). In another study, Bremner and colleagues reported no significant activation in ACC as well as decreased activation in ventral portions of ACC (subcallosal gyrus, Broadmann area 25) in PTSD (Bremner, Narayan et al., 1999; Bremner, Staib et al., 1999). Direct evidence for structural brain-associated differences of ACC in PTSD subjects comes from a study, in which the voxel-based morphometry showed a significant gray-matter volume reduction in the left ACC in trauma survivors with PTSD compared with those without PTSD (Yamasue et al., 2003). In another study, volumetric differences have also been demonstrated within the ACC and subcallosal cortex (SC) where the PTSD group (women with PTSD vs trauma-exposed women without PTSD) exhibited selectively decreased pregenual ACC and SC volumes (Rauch et al., 2003).

To date, the findings obtained by functional neuroimaging may allow only a limited number of conclusions: Taken together, the results of functional neuroimaging studies of the prefrontal cortex during trauma-related stimuli in PTSD are not yet conclusive. Several sources of evidence implicate regions in the prefrontal cortex and the higher order visual cortex as important components of the network that is sensitive to highly arousing emotional stimulation. These inconsistencies in the literature may arise from differences in patient populations, the neuroimaging method that has been used, and the method and strength of trauma-related stimuli (Matsuo et al., 2003). Furthermore, in several studies the anterior cingulate cortex (ACC) has been involved, although there are inconsistencies as to the nature of its involvement. One drawback of these studies, however, might be related to the differential involvement in different studies of the dorsal (‘cognitive’) versus rostral (‘affective’) subdivisions of the ACC (Bush, Luu, & Posner, 2000; Shin et al., 2001).

1.7.3 Emotion Information Processing in Schizophrenia: Evidence from empirical findings

Impaired emotional functioning, has been considered fundamental in schizophrenia (Bleuler, 1950). It manifests in flat, blunted, inappropriate affect and in depression (Kohler, Gur, & Gur, 2000). Bleuler has proposed that symptoms of schizophrenia could be classified into fundamental and accessory symptoms. According to Bleuler the fundamental impairment in schizophrenia includes symptoms such as ambivalence, disturbance of association, disturbance of affect, and a preference for fantasy over reality. The accessory symptoms include nearly all domains of function such as delusions, hallucinations, movement disturbances, somatic symptoms and manic and melancholic states. Intense interest in the last two decades has also been focused in schizophrenia research under plus or minus or positive and negative symptoms (Andreasen, 1982; Carpenter, Heinrichs, & Wagman, 1988; Crow, 1980; Harvey & Walker, 1987). One of the most pivotal deficits in the very early stages of the illness involves a reduction in emotional expression (affective blunting).

Emotional abnormalities are the most striking features of this illness. Although the mechanisms of emotional processing in schizophrenia have been less investigated than other aspects of the illness, a growing body of work has been applied to investigate the large-scale neural circuitry involved in emotion processing. Several brain regions have been implicated in emotion, suggesting a distributed network for emotion processing. This network includes areas in anterior, limbic/paralimbic regions, including the amygdala (Adolphs, Tranel, Damasio, & Damasio, 1995; Davis, 1992; LeDoux, 1992), ventral striatum (Haber & McFarland, 1999), anterior singulate cortex (Devinsky, Morrell, & Vogt, 1995), insula (Augustine, 1985) and orbitofrontal cortex (Rolls, 1996). Recent studies have used several experimental designs such as emotionally salient visual stimuli to investigate emotions and large-scale circuitry implicated in schizophrenia. In one study Crespo-Facorro et al., found that unmedicated schizophrenic patients exhibited less sensitivity to emotional pictures and therefore failed to activate limbic and paralimbic cortex (Crespo-Facorro et al., 2001). In another study, medicated schizophrenic patients passively viewing faces failed to activate the left amygdala and bilateral hippocampus (Gur et al., 2002).

Furthermore, responses during viewing mood congruent faces in unmedicated schizophrenic patients were also associated with failure of amygdala activation (Schneider et al., 1998). Results from a PET study indicated that unmedicated schizophrenia patients failed to activate neural systems, which are thought to support emotional processing during responses to pleasant and unpleasant visual stimuli (Paradiso et al., 2003) or to emotional faces (Phillips et al., 1999; L. M. Williams et al., 2004). These results strongly implicate a different network responding robustly to emotionally salient stimuli in schizophrenia patients, which might be a result of hypoactivity in distributed regions underlying schizophrenic disorders.

Furthermore, processing deficits in identification, discrimination, in recognition of expressions of facial emotions has been demonstrated by applying several paradigms (Edwards, Jackson, & Pattison, 2002; Streit, Ioannides et al., 2001). Specifically, a growing number of studies have observed that impairments in facial emotion perception in schizophrenia patients are most pronounced for threat-related expressions such as fear (Edwards et al., 2002; Mandal, Pandey, & Prasad, 1998). For example substantial insights into the impairments of facial affect recognition have come from one ERP study, where Streit et al. (Streit, Wolwer, Brinkmeyer, Ihl, & Gaebel, 2001) showed that schizophrenic patients as compared to healthy controls exhibited diminished scalp-recorded potentials. The amplitudes peaked at about 230 msec and potentials recorded at frontal electrode sites were linked with poorer task performance.

In another study Streit et al. by means of a 148-channel whole head MEG system obtained the response to facial expressions of emotions in fifteen partly remitted schizophrenia patients and twelve healthy volunteers (Streit, Ioannides et al., 2001). The neuromagnetic response to facial expressions of emotions revealed that patients exhibited weaker activations in inferior prefrontal, temporal, occipital and inferior parietal areas at circumscribed latencies.

Few functional imaging studies have investigated emotion processing in schizophrenia. However, most fMRI studies that have investigated responses in a mood induction experimental design patients did not show normal increases in amygdala activity during sad affect (Schneider et al., 1998) and in another fMRI study patients exhibited weaker activations at identifying emotions (Lee et al., 2002; Phillips et al., 1999). Changes in blood-oxygen-level-dependent (BOLD) responses where measured in fourteen schizophrenia patients and fourteen matched controls while viewing facial displays of emotions such as happiness, sadness, anger, fear, and disgust as well as neutral faces (Gur et al., 2002). BOLD responses detected by fMRI reflected changes as the subjects alternated between tasks of discriminating emotional valence (positive versus negative) and age (over 30 versus under 30) of the faces. The investigators found no evidence for differences between groups with regard to either task. Responses were associated for both tasks in controls with enhanced activity in the fusiform gyrus, occipital lobe, and inferior frontal cortex relative to the resting baseline condition. The increase was greater in the amygdala and hippocampus during the emotional valence discrimination task than during the age task. Schizophrenia patients exhibited in general weaker BOLD responses in response to both tasks. The investigators generated contrast maps between groups on the emotional valence discrimination task. Responsive voxels revealed significantly higher activation for the left amygdala and bilateral hippocampus in control subjects. This finding converges with the results from other fMRI studies using similar experimental designs that also found evidence for diminished activation in limbic areas in schizophrenia patients, related to emotional relevance of facial stimuli.

1.8 Research Aims and Hypotheses

In the first part, the present thesis examined the impact of childhood events on the psychiatric disorders in adulthood by documenting what is known about critical issues and theoretical concepts related to stressful life event research. The results of research reviewed above showed that the relationship between trauma and psychiatric illness, however, has begun to be explored fully during the last two decades. Based on studies of disruptions of attachment bonds in non-human primates (Finamore & Port, 2000), on animal models (De Kloet et al., 1988; Pynoos et al., 1996; Rasmusson & Charney, 1997) and numerous studies on exposure to trauma in persons with severe mental illness, a possible causal relationship between childhood abuse and adult psychopathology has been delineated (Coverdale & Turbott, 2000; Ellason & Ross, 1997; Golier et al., 2003). Furthermore, the evidence presented above, showing that stressful life events may have an impact on psychiatric diagnoses in adult life, supports the assumption that adolescence is an extremely critical phase in the development of later psychopathology (Maercker, Michael, Fehm, Becker, & Margraf, 2004; Schutzwohl & Maercker, 1999). Evidence suggests that it is difficult to assess the impact of childhood traumatic events on the psychiatric disorders in adulthood, as neither prospective research studies, nor experimental approaches are possible. Nevertheless, an increasing number of retrospective reports suggest that psychiatric disorders may be related to childhood psychological traumas such as neglect, physical or emotional abuse (J. C. Beck & van der Kolk, 1987; Bierer et al., 2003; Chu & Dill, 1991; Ellason & Ross, 1997; Herman et al., 1989; Mullen, Martin, Anderson, Romans, & Herbison, 1993). Based on the findings reported so far, it seems reasonable to posit a causal relationship between childhood abuse and adult psychopathology. In summary, the present study sets out to evaluate reported positive and negative life events from early childhood to adulthood in psychiatric patients. We addressed some of the above-mentioned problems by examining abuse histories across a range of several psychiatric diagnoses within a controlled cross-national design. In the present study (study I) a German/Swiss and a Romanian psychiatric group have been included, in order to determine whether reports vary between cultural backgrounds. In summary, in a first part the present thesis has sought to examine whether:

(a) Negative life experiences are positively associated with psychiatric diagnoses in adulthood, and

(b) Early childhood and adolescence were 'sensitive periods', that is, whether psychiatric diagnoses were more closely related to negative experience in these developmental periods developmental periods

In order to examine these questions, one study, namely study I has been conducted, using specific variables that are hypothesized to moderate the suggested relationships between negative and positive life events across developmental span and later psychopathology in adulthood.

In the second part of the present thesis, evidence cited so far has highlighted the fact that exposure to severe stress and chronic stress especially in PTSD patients can have devastating changes in humans' allostasis. The physiologic systems activated by stress can not only protect and restore but also damage the body (McEwen, 2004). Of particular interest in the second part of the present thesis are emotional deficits associated with PTSD. Disrupted emotional experiences are central features of the long-term consequences of traumatic events. This final issue has been approached in the present thesis by reviewing contemporary emotion theories that are particularly relevant to the question examined in the present thesis (Damasio et al., 1994; P. J. Lang, 1979; P. J. Lang, Bradley et al., 1998b; LeDoux, 1995).

In this sense, it has been demonstrated that photographic images from the IAPS evoke a broad range of emotional reactions, varying in intensity and involving both pleasant and unpleasant affect (P. J. Lang, Bradley, Cuthbert, & Patrick, 1993). Of course, looking at affective pictures in a laboratory setting does not correspond to real life events, thus making overt reactions barely possible. However, the varying degrees of symbolic threat induced by aversive slides are sufficient to elicit a cascade of defensive motivation, especially in PTSD patients (P. J. Lang, 1995). Furthermore, experimental evidence in this area has shown that behaviors elicited in the context of emotional picture perception co-vary with motivational parameters(P. J. Lang, Bradley et al., 1998a). The last decade's neuroscientific research has begun to delineate the neural mechanisms by which the brain responds to emotional stimuli (Lane, Reiman et al., 1997; P. J. Lang, Bradley, Fitzsimmons et al., 1998). Neuroimaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have been used to map brain regions associated with the visual processing of emotional in healthy participants (Lane et al., 1999; Lane, Fink, Chau, & Dolan, 1997; Lane, Reiman et al., 1997; P. J. Lang, Bradley, Fitzsimmons et al., 1998; Reiman et al., 1997; Schneider et al., 1999). Studies involving patients with lesions (Bechara, Damasio, Damasio, & Anderson, 1994; Morris, Friston et al., 1998; Saver & Damasio, 1991) and animals with experimental lesions (D. C. Blanchard & Blanchard, 1972; LeDoux, 1992, 1995) have consistently identified several brain circuits: the amygdala, hippocampus, anterior cingulate, and the neocortex, including sensory cortices, as being crucial for affective modulation of visual perception. Although there has been considerable empirical research conducted on cortical activation patterns during emotional stimulation however, so far no study has investigated MEG correlates of affective picture processing in a representative sample of PTSD patients. More precisely, we did compare PTSD patients with a clinical group of schizophrenia patients and with a control group with no mental disorders diagnosis. Based on findings reported so far, it seems reasonable therefore to assume that PTSD subjects who have a persisting conditioned emotional response (startle reaction) to stimuli reminiscent of the traumatic event would demonstrate different magneto-cortical activity measured in the context of emotional stimulation as compared to schizophrenia patients and to control subjects. In summary, the present thesis namely studies II and III aimed at examining the following experimental questions:

(1) Could emotional traumatic experience in PTSD patients modify visual processing already at early stages of visual information processing?

(2) Is there a specific enhancement of the magnetic field in response to high arousing (pleasant and unpleasant) as compared to neutral emotional pictures in PTSD? Is this differed responding reflected in modulation of event-related magnetic fields?

(3) Emotional modulation of the eye-blink and visceral responses to an acoustic startle probe. Specific autonomic (e.g., heart rate change) and somatic reflexes (e.g., startle change) in the fear-network of PTSD patients?

(4) What are the brain regions contributing to process of emotional modulation in PTSD patients? Are there any differences in the fear-network of PTSD patients?

In order to examine these questions, one experiment of affective picture processing have been conducted, were high (pleasant and unpleasant)- and low (neutral)-arousing pictures in a visual evoked magnetic field paradigm while recording the magnetoencephalogram. In this experiment, magnetocortical activity was monitored in 15 PTSD patients, 15 schizophrenia patients and 12 healthy participants.

Methods

Chapter 2

Study I

[1]Negative and positive childhood experiences across developmental periods in psychiatric patients with different diagnoses – an explorative study

2.1 Summary

A high frequency of childhood abuse has often been reported in adult psychiatric patients. The present survey explores the relationship between psychiatric diagnoses and positive and negative life events during childhood and adulthood in psychiatric samples. A total of 192 patients with diagnoses of alcohol-related disorders (n=45), schizophrenic disorders (n=52), affective disorders (n=54), and personality disorders (n=41) completed a 42-item self-rating scale (Traumatic Antecedents Questionnaire, TAQ). The TAQ assesses personal positive experiences (competence and safety) and negative experiences (neglect, separation, secrets, emotional, physical and sexual abuse, trauma witnessing, other traumas, and alcohol and drugs abuse) during four developmental periods, beginning from early childhood to adulthood. Patients were recruited from four Psychiatric hospitals in Germany, Switzerland, and Romania; 63 subjects without any history of mental illness served as controls. The amount of positive experiences did not differ significantly among groups, except for safety scores that were lower in patients with personality disorders as compared to the other groups. On the other side, negative experiences appeared more frequently in patients than in controls. Emotional neglect and abuse were reported in patients more frequently than

[1] This part of the thesis largely corresponds to: Saleptsi E, Bichescu D, Rockstroh, B, Neuner F, Schauer E, Studer K, Hoffmann K, Elbert, T. *Negative and positive childhood experiences across developmental periods in psychiatric patients with different diagnoses - an explorative study*. BMC Psychiatry. 2004 Nov 26;4(1):40.

physical and sexual abuse, with negative experiences encountered more often in late childhood and adolescence than in early childhood. The patients with alcohol-related and personality disorders reported more negative events than the ones with schizophrenic and affective disorders. The present findings add evidence to the relationship between retrospectively reported childhood experiences and psychiatric diagnoses, and emphasize the fact that a) emotional neglect and abuse are the most prominent negative experiences, b) adolescence is a more ‘sensitive’ period for negative experiences as compared to early childhood, and c) a high amount of reported emotional and physical abuse occurs in patients with alcohol-related and personality disorders respectively.

2.2 Introduction

It is difficult to assess the impact of childhood traumatic events on the psychiatric disorders in adulthood, as neither prospective research studies, nor experimental approaches are possible. Nevertheless, an increasing number of retrospective reports suggest that psychiatric disorders may be related to childhood psychological traumas such as neglect, physical or emotional abuse (J. C. Beck & van der Kolk, 1987; Briere & Zaidi, 1989; Chu & Dill, 1990; Ellason & Ross, 1997; Herman et al., 1989; Mullen et al., 1993). In particular, significant correlations between the severity of psychiatric symptoms and that of stressful and traumatic experiences during childhood were found (Bryer, Nelson, Miller, & Krol, 1987; Grilo, Sanislow, Fehon, Martino, & McGlashan, 1999; Lange et al., 1999; Powell, 1994; Read, 1998; Wurr & Partridge, 1996). Reports of physical and sexual abuse in childhood are more frequent in psychiatric patients than in the healthy population (Carmen, Rieker, & Mills, 1984; Jacobson & Richardson, 1987; Palmer, 1992; Swett, Surrey, & Cohen, 1990); among these are patients diagnosed with affective disorders (Gladstone, Parker, Wilhelm, Mitchell, & Austin, 1999; Hyun, Friedman, & Dunner, 2000; Levitan et al., 1998), somatization disorders (Morrison, 1989; Pribor, Yutzy, Dean, & Wetzel, 1993; Saxe et al., 1994), borderline personality disorders (Bryer et al., 1987; Craine et al., 1988; Herman et al., 1989; Shearer, Peters, Quaytman, & Ogden, 1990; Zanarini et al., 2002), substance-related disorders (Langeland & Hartgers, 1998; Moncrieff, Drummond, Candy, Checinski, & Farmer, 1996; Windle, Windle, Scheidt, & Miller, 1995), and schizophrenic disorders (Norman & Malla, 1993; Read, 1997; Resnick et al., 2003). Specifically, several studies have documented high rates of trauma in individuals with severe mental illness (Goodman et al., 1997). For a sample of schizophrenic women, Friedmann and Harisson (1984) reported that 60% of them had suffered childhood sexual abuse (S. Friedman & Harrison, 1984). Abused patients displayed more pronounced symptoms such as hallucinations (Heins, Gray, & Tennant, 1990; Read & Argyle, 1999) and delusions (Goff, Brotman, Kindlon, Waites, & Amico, 1991).

Any conclusion to such reports, however, must be drawn by taking into consideration that the validity of childhood memories, particularly in psychiatric patients, may be questioned, as the range of childhood traumas indexed in these studies is generally limited, and often only childhood sexual abuse is targeted. Moreover, the observed relationships are correlational in nature, and do not justify the conclusion that childhood trauma favors the development of psychiatric disorders. Antecedents of developing psychopathology may also provoke certain parental behavior. Also, a third variable, such as social conditions, may have caused both childhood abuse and later pathological development. Another notable finding is that the prevalence rates of antecedent traumatic events vary considerably across studies. This may be due to different definitions of abuse which include more detailed (Carmen et al., 1984) or more global (Craine et al., 1988) descriptions. Furthermore, the amount of psychosocial elements such as neglect, family disturbance, the nature of preexisting and subsequent attachment patterns, special competencies, etc., is difficult to be assessed or taken into account. Only a limited number of studies (Palmer, Bramble, Metcalfe, Oppenheimer, & Smith, 1994; Palmer, Coleman, Chaloner, Oppenheimer, & Smith, 1993) have so far included control groups, allowing one to compare self-reports of abusive sexual experiences during childhood in psychiatric patients to those in the healthy population. There is also a lack of research studies that assess these issues within different cultural backgrounds.

The present study sets out to evaluate reported positive and negative life events from early childhood to adulthood in psychiatric patients. We addressed some of the above-mentioned problems by examining abuse histories across a range of several psychiatric diagnoses within a controlled cross-national design. We sought to examine whether (a) negative life experiences are positively associated with psychiatric diagnoses in adulthood, and (b) early childhood and adolescence were 'sensitive periods', that is, whether psychiatric diagnoses were more closely related to negative experience in these developmental periods.

The present study includes a German/Swiss and a Romanian psychiatric group, in order to determine whether reports vary between cultural backgrounds.

2.3 Methods and Materials

Subjects

Patients were recruited from four Psychiatric Hospitals within two different cultural settings, Switzerland/Southern Germany versus the Moldavia region in Romania: the Center for Psychiatry Reichenau and the Center for Psychiatry Weissenau in Germany, the Psychiatric Hospital Münsterlingen in Switzerland, and the Psychiatric Hospital "Socola", Jassy in Romania. A total of 192 psychiatric inpatients (98 German and 94 Romanian psychiatric patients, range 18-78 years) filled in the questionnaire. Sixty-three control subjects without any history of psychiatric diagnosis were recruited from the clinical staff and the university employees (Konstanz in Germany, Jassy in Romania) as controls (38 Germans and 25 Romanians). The control subjects have been simply inquired whether they had any stationary hospitalization in the psychiatry; no further assessments have been done. After a full explanation of the study, written informed consent was obtained from all subjects.

By considering the clinician-made diagnoses which were written down from the medical files available in the psychiatric clinics the patients were recruited from, the patients were distributed in four diagnostic groups: alcohol-related disorders (n=45), schizophrenic disorders (n=52), affective disorders (n=54), and personality disorders (n=41). At all psychiatric clinics in Germany/Switzerland and Romania the diagnoses were made according to the ICD-10 criteria. Within our patient groups, the following lifetime mental disorders were assessed by using the ICD-10: alcohol-related disorders (dependence syndrome, psychotic and unspecified mental disorders due to the use of alcohol), schizophrenic disorders (paranoid schizophrenia, schizoaffective disorder, and undifferentiated schizophrenia), affective disorders (bipolar depressive disorders, recurrent depressive disorder, cyclothymia, and dysthymia), and personality disorders (borderline, schizoid, paranoid, histrionic, dissocial, and dependent personality disorder respectively). A few patients within our sample were diagnosed with comorbid symptoms: 4 patients with affective disorders had symptoms of substance abuse and 7 of them had anxiety symptoms; also, within the schizophrenic disorders group, 2 patients had symptoms of alcohol abuse and 6 had depressive symptoms. There were also patients who received two diagnoses: one of which was a personality disorder (i.e., 5 patients with affective disorders, 7 with alcohol-related disorders, and 2 with schizophrenic disorders). In these cases, we considered the other diagnosis for the distribution into the diagnostic groups.

Table 2.1 summarizes the demographical characteristics of all subjects. The patient groups were similar with respect to the psychiatric history. There were differences among groups concerning gender distribution, age, and education. The gender-distribution differences among groups were due to the high number of women within the control and the affective disorders groups. With regard to the noted age differences, the patients with affective and alcohol-related disorders respectively had higher mean age as compared to all the other groups. The education differences among groups are only due to the lower educational level in patients with alcohol-related disorders. Romanian patients with affective disorders had a longer psychiatric history than the German/Swiss ones [t(51) = 2.3, p < 0.05]. Regarding gender distribution and the average duration of education, the German/Swiss and Romanian diagnostic groups were similar. The German/Swiss controls were significantly older than the Romanian ones [t(43) = 4.4, p < 0.001] and the German/Swiss patients with alcohol-related disorders were significantly younger than the Romanian ones [t(61) = 3.5, p < 0.001].

	Alcohol Related Disorders		Schizophrenic Disorders		Affective Disorders		Personality Disorders		Controls			
	G/S	R	G/S	R	G/S	R	G/S	R	G/S	R	Analysis	
	N		N		N		N		N		χ^2	p
Gender											12	<.05
Female	6	10	10	11	14	19	11	6	23	15		
Male	14	15	18	13	10	11	15	9	15	10		
	Mean ± SD		Mean ± SD		Mean ± SD		Mean ± SD		Mean ± SD		F	p
Age	**31±9**	**45±12**	34±8	36±10	40±12	44±8	34±8	32±11	**38±13**	**28±7**	6	<.001
Education	2±1	2±1	3±1	3±1	3±1	3±1	2±1	3±1	3±1	3±1	4	<.01
Psychiatric history (yrs)	6±1	7±10	8±9	11±10	**4±6**	**9±9**	4±5	6±7	-	-	2	n.s.

Table 2.1: Demographic characteristics of the control and of the patient groups.[1, 2]

[1] Abbreviations: G/S: German/Swiss; R: Romanian; Education: 0 = no education, 1= school for the mentally challenged, 3 = middle school, 4 = high school;
[2] Areas where the values are written with bold characters indicate significant differences between German/Swiss and Romanian subjects within the diagnostic groups (i.e., alcohol-related disorders, schizophrenic disorders, affective disorders, personality disorders and control group respectively).

Material

Life experiences were assessed with the Traumatic Antecedents Questionnaire (TAQ) (Herman & van der Kolk, 1987). The TAQ is a 42-item self-rating questionnaire, which covers 11 subscales enquiring into the severity of positive (i.e., competence and safety) and negative experiences (i.e., neglect, separation, secrets, emotional abuse, physical abuse, sexual abuse, witnessing, other traumas, and alcohol and drugs) during four developmental periods (ages 0-6, 7-12 13-18, and ≥19). Each subscale includes 2-6 items. Each item requires the occurrence of a certain type of experience for each of the different age periods. The subjects were asked to score on a frequency/intensity scale the degree to which it describes their experience: 0 (“never or not at all”), 1 (“rarely or a little bit”), 2 (“occasionally or moderately”), 3 (“often or very much”), and DK (“don’t know”). In a subsequent step, the average scores were calculated within each developmental period for each of the 11 subscales.

The procedure we used was the following: first, the “don’t know” responses were noted in a non-numerical manner, by using asterisks (*) to indicate missing values and these values were counted as 0; secondly, the response scores were added up and the sum was divided by the total number of items within the subscale in that age period for which there were numerical scores. By using this procedure, we excluded “don’t know” responses from the total scores calculation.

Data analysis

Comparisons of demographic data were made with analysis of variance (ANOVA) and with two-tailed unpaired t-tests for continuous variables. Chi-square analysis was used to compare nominal data. The differences between groups were evaluated individually for each TAQ scale by repeated-measures ANOVA with the cultural background (German/Swiss versus Romanian), psychiatric status (alcohol-related disorders, schizophrenic disorders, affective disorders, personality disorders or controls), and gender (female versus male) as between-subjects factors, and developmental period (4 periods) as within-subjects factor. The probability level for rejecting the null hypothesis was set at $P < 0.05$. Post-hoc comparisons were carried out to evaluate main effects and interactions using Bonferroni/Dunn tests. A principal components analysis was also applied to the entire sample in order to identify those factors, which could account for individual variability across the eleven scales of the TAQ. The principal components were derived by using varimax rotation to orthogonalize solutions.

2.4 Results

Positive experiences

Table 2.2 lists group mean scores on each of the two positive experiences scales. The patients generally exhibited lower mean scores on reported positive experiences as compared to the controls. The reported level of *competence* did not differ between diagnostic groups [F(4,198) = 0.8, n.s] or cultural samples [F(1,198) = 0.1, n.s]. A main effect of developmental period [F(3,594) = 25.7, P < 0.001] was explained by the increase of competence from early childhood to adolescence (P < 0.05), and by the decrease of competence in adulthood as compared to adolescence (P < 0.05).

For both cultural samples, patients with personality disorders reported lower values on the *safety* subscale than any of the other groups [F(4,215) = 4.5, P < 0.01]. Post hoc tests showed that patients with personality disorders (P < 0.001) and those with affective disorders (P < 0.01) reported less such experiences as compared to the controls. The reported level of safety increased through adolescence [F(3,645) = 11.1, P < 0.001], but the interaction of the developmental period with the psychiatric status revealed a decrease in safety accounts from the age of 13-18 years towards adulthood in all patient groups [F(12,645) = 2.8, P < 0.001].

Positive Experiences and Age at Onset	Alcohol Related Disorders	Schizophrenic Disorders	Affective Disorders	Personality Disorders	Control Group	Analysis	
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	F	p
Early Childhood (0-6)							
Competence	1.5±0.9	1.9±0.9	1.7±1.0	1.7±0.9	1.7±0.1	0.7	n.s
Safety	1.4±0.8	1.7±0.8	1.6±0.8	1.2±0.8	1.6±0.7	3.2	<.05
Latency (7-12)							
Competence	2.1±0.8	2.0±0.8	2.1±0.7	1.9±0.8	2.1±0.9	0.2	n.s
Safety	1.8±0.8	1.8±0.8	1.9±0.7	1.3±0.7	1.9±0.7	5.1	<.001
Adolescence (13-18)							
Competence	2.1±0.9	2.1±0.7	2.2±0.6	2.1±0.8	2.3±0.8	0.6	n.s
Safety	1.9±0.8	1.7±0.8	1.8±0.8	1.3±0.8	2.0±0.8	4.0	<.01
Adulthood (≥19)							
Competence	1.9±1.0	1.8±0.8	2.1±0.8	2.0±0.8	2.2±0.8	1.3	n.s
Safety	1.7±0.8	1.7±0.8	1.7±0.8	1.5±0.7	2.1±0.7	4.9	<.001

Table 2.2: Mean scores of positive experiences across developmental periods among all groups.

Negative experiences

Table 2.3 shows the mean scores of traumatic experiences for all patient groups and for the control group across developmental periods. Negative experiences were more frequent in patients than in controls as indicated by significant main effects of the psychiatric status on each of the nine subscales. In addition, there was an important increase of amount of reported negative experiences across developmental periods.

Negative Experiences and Age at Onset	Alcohol Related Disorders	Schizophrenic Disorders	Affective Disorders	Personality Disorders	Control Group	Analysis	
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	F	p
Early Childhood (0-6)							
Neglect	0.6±0.5	0.7±0.7	0.5±0.5	0.8±0.6	0.2±0.3	8.1	<.001
Separation	0.5±0.6	0.4±0.5	0.4±0.6	0.6±0.8	0.2±0.4	3.9	<.01
Secrets	0.9±0.9	1.2±1.1	1.0±0.9	1.4±1.1	0.6±0.7	4.8	<.01
Emotional Abuse	0.7±0.6	1.0±1.0	0.7±0.8	1.2±0.9	0.3±0.5	8.2	<.001
Physical Abuse	0.4±0.6	0.4±0.5	0.3±0.5	0.7±0.7	0.1±0.3	5.7	<.001
Sexual Abuse	0.0±0.3	0.2±0.6	0.1±0.3	0.3±0.6	0.1±0.4	2.0	n.s.
Trauma Witnessing	0.4±0.5	0.4±0.5	0.5±0.6	0.7±0.9	0.1±0.2	7.6	<.001
Other Traumas	0.4±0.5	0.3±0.4	0.2±0.4	0.4±0.6	0.2±0.3	3.1	<.05
Alcohol/Drug Abuse	0.4±0.8	0.3±0.6	0.5±0.7	0.5±0.7	0.1±0.2	4.0	<.01
Latency (7-12)							
Neglect	0.7±0.6	0.8±0.7	0.7±0.5	1.1±0.8	0.5±0.5	5.0	<.001
Separation	0.6±0.7	0.5±0.6	0.6±0.7	0.9±0.8	0.5±0.6	2.8	<.05
Secrets	1.0±0.9	1.2±0.1	1.1±0.9	1.6±1.1	0.8±0.8	4.2	<.01
Emotional Abuse	0.8±0.6	1.1±0.9	1.0±0.8	1.4±0.9	0.7±0.8	4.6	<.01
Physical Abuse	0.5±0.7	0.6±0.7	0.6±0.6	0.9±0.8	0.5±0.6	2.5	<.05
Sexual Abuse	0.1±0.3	0.2 ±0.5	0.1±0.2	0.5±0.8	0.1±0.4	5.3	<.001
Trauma Witnessing	0.5±0.6	0.5±0.5	0.7±0.6	0.9±0.8	0.4±0.5	5.5	<.001
Other Traumas	0.4±0.5	0.4±0.4	0.4±0.5	0.5±0.6	0.3±0.4	1.4	n.s.
Alcohol/Drug Abuse	0.5±0.7	0.3±0.6	0.6±0.7	0.6±0.8	0.2±0.4	4.1	<.01
Adolescence (13-18)							
Neglect	1.0±0.6	0.9±0.7	1.0±0.5	1.2±0.7	0.8±0.6	2.5	<.05
Separation	0.9±0.8	0.8±0.8	0.9±0.7	0.9±0.7	0.6±0.7	2.4	<.05
Secrets	1.1±0.9	1.3±1.0	1.1±0.9	1.5±1.0	0.7±0.8	4.7	<.01
Emotional Abuse	0.8±0.6	1.3±0.9	1.1±0.7	1.4±0.9	0.8±0.8	4.6	<.01
Physical Abuse	0.8±0.7	0.5±0.6	0.5±0.6	1.0±0.9	0.5±0.6	5.0	<.001
Sexual Abuse	0.2±0.4	0.2±0.4	0.2±0.4	0.5±0.8	0.1±0.3	3.2	<.05
Trauma Witnessing	0.6±0.6	0.5±0.5	0.7±0.6	1.0±0.8	0.4±0.5	5.9	<.001
Other Traumas	0.6±0.6	0.5±0.5	0.4±0.5	0.6±0.5	0.3±0.3	3.4	<.05
Alcohol/Drug Abuse	1.1±1.0	0.6±0.8	0.7±0.9	0.9±0.8	0.4±0.7	5.3	<.001
Adulthood (19≥)							
Neglect	1.4±0.8	1.3±0.9	1.2±0.7	1.2±0.8	0.9±0.7	3.0	<.01
Separation	1.6±0.7	1.1±0.9	1.5±0.8	1.2±0.9	1.0±0.7	4.3	<.01
Secrets	1.1±1.0	1.3±1.1	1.2±0.9	1.6±0.9	0.5±0.7	8.1	<.001
Emotional Abuse	0.9±0.7	1.2±0.9	1.1±0.9	1.4±0.9	0.6±0.6	6.8	<.001
Physical Abuse	1.0±0.9	1.0±0.8	0.9±0.9	1.0±0.9	0.4±0.6	5.1	<.001
Sexual Abuse	0.3±0.6	0.6±0.8	0.4±0.7	0.5±0.7	0.2±0.4	2.8	<.05
Trauma Witnessing	0.8±0.6	0.7±0.7	1.0±0.8	1.0±0.9	0.5±0.4	4.3	<.01
Other Traumas	1.2±0.6	1.0±0.7	1.1±0.8	1.0±0.6	0.4±0.4	14.8	<.001
Alcohol/Drug Abuse	2.1±0.8	0.8±0.9	1.1±0.9	1.0±0.9	0.3±0.6	29.3	<.001

Table 2.3: Mean scores of negative experiences among all groups.

With respect to the experiences of *neglect*, the psychiatric patients reported higher rates than the controls [F(4,214) = 5.7, P < 0.001], the post hoc tests revealing that all patient groups reported more such experiences as compared to the controls: patients with personality disorders (P < 0.001), alcohol-related disorders (P < 0.05), schizophrenic disorders (P < 0.05), and affective disorders (P < 0.05). There was an increase of the amount of reported neglect experiences across developmental periods [F(3,642) = 91.5, P < 0.001]. Across developmental periods there were significant effects of the psychiatric status [F(12,642) = 3.2, P < 0.001]: the post hoc tests showed that patients with personality disorders (P < 0.001) and with alcohol-related disorders (P < 0.01) reported a highly significant increase of the amount of neglect experiences across developmental periods as compared to the controls (Figure 2.1).

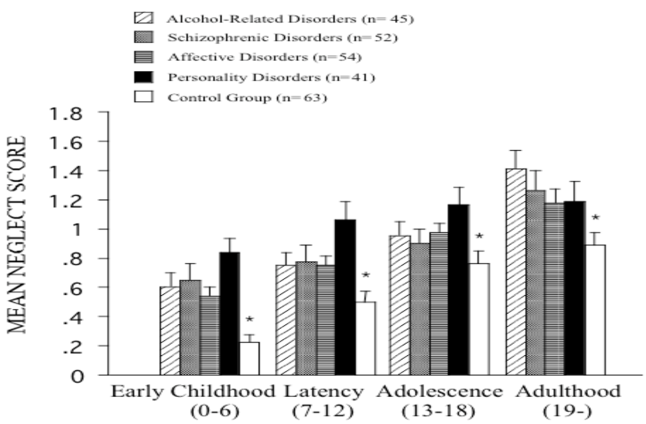

Figure 2.1: Mean neglect score across developmental periods among all groups. The psychiatric patients reported higher rates than the controls [F(4,214) = 5.7, P < 0.001]. There was an increase of the amount of reported neglect experiences across developmental periods [F(3,642) = 91.5, P < 0.001]. Error bars stand for standard error of the mean. Asterisks indicate significant main effects of the psychiatric status.

Irrespective of the psychiatric status and developmental periods, Romanian subjects generally reported a higher amount of neglect experiences, as shown by the main effect of the cultural background [$F(1,214) = 6.4$, $P < 0.05$]. Romanian patients, particularly those with schizophrenic disorders, reported a higher incidence of neglect experiences than their German counterparts ($P < 0.01$), as revealed by the interaction between the psychiatric status and cultural background [$F(4,214) = 5.6$, $P < 0.001$]. As indicated by the interaction between the developmental period and the cultural background, the mean scores of neglect experiences were higher in the Romanian sample as compared to the German/Swiss one for the earliest (0-6 years) period [$F(3,642) = 5.3$, $P < 0.001$].

Separation: Patients, particularly those with alcohol-related disorders, personality disorders, and affective disorders reported more often separation experiences than controls [$F(4,227) = 3.3$, $P < 0.01$, $P < 0.01$ for post-hocs]. Mean scores on separation increased with age, and were highest in adulthood [$F(3,681) = 103.0$, $P < 0.001$].

Secrets: Higher patient mean scores were confirmed by the main effect of the psychiatric status [$F(4,182) = 6.8$, $P < 0.001$], especially for those with personality disorders ($P < 0.001$) and with schizophrenic disorders ($P < 0.001$), as revealed by post-hoc tests. There was also an indication of sensitivity to the cultural background [$F(1,182) = 7.5$, $P < 0.01$], as there was an increase in these scores in the Romanian sample, irrespective of the diagnosis and developmental period.

Emotional abuse was more frequently reported by patients than by controls [$F(4,194) = 7.0$, $P < 0.001$] and more frequently by patients with personality disorders ($P < 0.01$) and by schizophrenic patients ($P < 0.05$) than the ones with a history of alcohol-related disorders (Figure 2.2). A main effect of the developmental period [$F(3,582) = 24.0$, $P < 0.001$] was explained by an increase of the reported emotional abuse from early childhood to adolescence ($P < 0.05$), and a decrease in adulthood ($P < 0.05$) were noted. Similar to the case of the neglect experiences, the Romanian sample scored also higher than the German/Swiss sample, mainly for the earliest (0-6 yr.) period, as revealed by the interaction between the development period and the cultural background [$F(3,582) = 5.4$, $P < 0.01$].

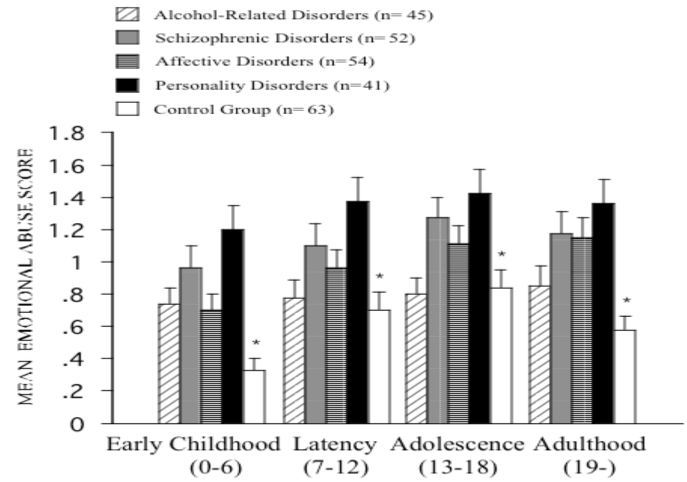

Figure 2.2: Mean emotional abuse score across developmental periods among all groups. Emotional abuse was more frequently reported by patients than by controls [$F(4,194) = 7.0$, $p < 0.001$]. A main effect of the developmental period [$F(3,582) = 24.0$, $P < 0.001$] was explained by an increase of the reported emotional abuse from early childhood to adolescence, and a decrease in adulthood were noted. Error bars stand for standard error of the mean. Asterisks indicate significant main effects of the psychiatric status.

Irrespective of the developmental period, *physical abuse* was more often reported by patients with personality disorders [$F(4,202) = 5.7$, $P < 0.001$] (Figure 2.3). Post-hoc comparisons also revealed higher rates of physical abuse reports among patients with alcohol-related disorders ($P < 0.01$) and with schizophrenic disorders ($P < 0.05$) than among controls. The reports of physical abuse generally increased across developmental periods, with adulthood as the most susceptible period of such reports [$F(3, 606) = 35.1$, $P < 0.001$]. The interaction of the developmental period with the psychiatric status showed that this increase in physical abuse reports across developmental periods was mainly to be remarked in patients [F(12,606) = 3.0, P < 0.001].

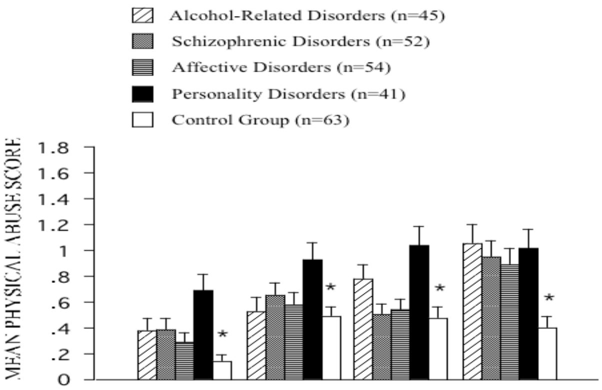

Figure 2.3: Mean physical abuse score across developmental periods among all groups. Physical abuse was more often reported by patients with personality disorders [F(4,202) = 5.7, P < 0.001].The reports of physical abuse generally increased across developmental periods, with adulthood as the most susceptible period of such reports [F(3, 606) = 35.1, P < 0.001]. Error bars stand for standard error of the mean. Asterisks indicate significant main effects of the psychiatric status.

Sexual abuse (Figure 2.4) was primarily reported by patients, and not by controls [F(4,205) = 5.2, P < 0.001], and particularly by patients with personality disorders (P < 0.001). Higher rates of sexual abuse were reported among patients with alcohol-related disorders (P < 0.01), with schizophrenic disorders (P < 0.05), and with affective disorders (P < 0.05) than among controls as shown by post-hoc tests. If sexual abuse was experienced, it occurred particularly in later developmental periods [F(3,615) = 20.4, P < 0.001]. Sexual abuse was more often experienced by female patients [F(1,205) = 10.0, P < 0.001] after puberty [F(3, 615) =10.0, P < 0.001], as revealed by the interaction between the developmental period and gender. We also found a 3-way interaction between the developmental period, psychiatric status and cultural background [F(12,615) = 2.6, P < 0.01). The interaction between the developmental period and cultural background revealed that Romanian but not German/Swiss schizophrenics reported more frequently sexual abuse particularly in adulthood [F(3,615) = 5.0, P < 0.01].

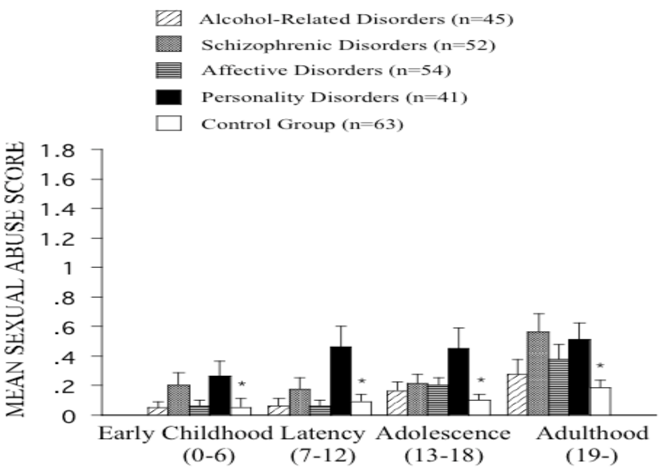

Figure 2.4: Mean sexual abuse score across developmental periods among all groups. Sexual abuse was primarily reported by patients, and not by controls, and particularly by patients with personality disorders [F(4,205) = 5.2, P < 0.001]. If sexual abuse was experienced, it occurred particularly in later developmental periods [F(3,615) = 20.4, P < 0.001]. Error bars stand for standard error of the mean. Asterisks indicate significant main effects of the psychiatric status.

Trauma witnessing was reported most often by patients with personality disorders as compared to all other groups [$F(4,209) = 8.0$, $P < 0.001$]. Post-hoc tests showed that patients with affective disorders ($P < 0.01$) and with alcohol-related disorders ($P < 0.05$) also reported more experiences of trauma witnessing than the controls. Irrespective of the diagnosis, Romanian patients, but not controls, reported higher mean scores on this variable and more often than their German/Swiss counterparts [$F(1,209) = 17.0$, $P < 0.001$]. The interaction between the cultural background and developmental period indicated in the Romanian sample an increase of trauma witnessing in adulthood [$F(3,627) = 8.0$, $P < 0.001$].

Other traumas: Similar to the pattern of trauma witnessing, all patients reported a greater number of traumatic events than the control group [$F(4,211) = 8.0$, $P < 0.001$]: alcohol-related disorders ($P < 0.001$), personality disorders ($P < 0.001$), schizophrenic disorders ($P < 0.01$), and affective disorders ($P < 0.01$), as explained by post-hocs. An increase in the amount of other traumas reports across the developmental periods with highest values in adulthood for all patient groups [$F(12, 633) = 7.0$, $P < 0.001$] was also revealed.

Alcohol and Drug abuse: As previously expected, patients treated for alcohol-related disorders reported more alcohol and drug abuse than all the other groups [$F(4,213) = 12.3$, $P < 0.001$]. The post-hoc tests showed that the other patient groups also reported more alcohol and drug abuse when compared to the control group: affective disorders ($P < 0.001$), personality disorders, ($P < 0.001$) and schizophrenic disorders ($P < 0.05$). As also anticipated, abuse increased across developmental periods until adulthood [$F(3,639) = 110.0$, $P < 0.001$], particularly in patients with alcohol-related disorders, as revealed by the interaction between the developmental period and psychiatric status [$F(12,639) = 14.3$, $P < 0.001$]. Irrespective of the diagnosis, Romanian patients, but not controls, showed higher mean scores on reporting alcohol and drug abuse than their German/Swiss counterparts [$F(4,213) = 3.4$, $P < 0.01$], as shown by the interaction between the psychiatric status and cultural background. Compared to the German group, alcohol and drug abuse in the Romanian sample was higher, particularly in adulthood [$F(3,639) = 9.8$, $P < 0.001$].

Interrelations

A principal components factor analysis was performed to explore interrelationships among TAQ subscales. The results of this analysis indicated that the most appropriate solution involved five factors that jointly accounted for 56.2% of the total variance in the dataset. Table 2.4 summarizes the results of the varimax rotation for the five-factor solution. The first factor showed high positive loadings on *physical abuse, sexual abuse, trauma witnessing, and other traumas*, obviously explains the traumatic experiences. The second factor showed high positive loadings on *competence* and *safety*, apparently accounting for variance attributed to positive experiences. The third factor showed high positive loadings on the *first year of illness* with *alcohol and drug abuse*. The fourth factor, consisting of *separation*, evidently explains disruptions of attachment. The fifth factor, which included *secrets* and *emotional abuse*, appeared to account for family chaos. Thus, the structure of the study instrument was well reproduced for the present sample, which included different psychiatric diagnoses and different cultural backgrounds.

	Factor Loading[2]				
Variables	FACTOR 1: Traumatic Experiences[3]	FACTOR 2: Positive Experiences[4]	FACTOR 3: Vulnerability to Alcohol Abuse[5]	FACTOR 4: Disruptions of Attachment[6]	FACTOR 5: Family Chaos[7]
Competence	-0.0	**0.8**	0.2	0.1	0.1
Safety	0.2	**0.8**	-0.0	0.0	-0.2
Neglect	0.2	-0.3	0.1	-0.0	0.3
Separation	0.4	0.2	-0.0	**0.8**	0.1
Secrets	-0.0	-0.1	-0.0	0.1	**0.7**
Emotional Abuse	0.2	0.0	0.6	-0.0	**0.6**
Physical Abuse	**0.7**	-0.0	-0.0	0.0	0.0
Sexual Abuse	**0.4**	0.0	0.0	-0.6	0.1
Witnessing	**0.6**	0.0	-0.0	0.0	0.2
Other Traumas	**0.6**	0.2	0.1	0.2	0.1
Alcohol & Drug Abuse	0.4	-0.2	**0.5**	0.0	-0.3
First Year of Illness	-0.1	0.1	**0.8**	-0.1	0.2

Table 2.4: Varimax solution with five factors for negative and positive childhood experiences across developmental periods in psychiatric patients with different diagnoses.[1]

1 Total percent of variance = 56.2%

2 Shaded areas indicate specific domains of the TAQ contributing to each factor

3 Eigenvalue=4.88; percent of variance = 40.7%

4 Eigenvalue=1.476; percent of variance = 12.3%, 5 Eigenvalue=1.013; percent of variance = 8.4%, 6 Eigenvalue=0.835; percent of variance = 7.0%,

7 Eigenvalue=0.815; percent of variance = 6.8%

2.5 Discussion

The study aimed at exploring whether psychiatric diagnoses, e.g. alcohol-related disorders, schizophrenic disorders, affective disorders, and personality disorders are related to retrospectively reported positive and negative life events across developmental periods, and if so, whether special developmental periods are characterized by more negative experiences than others.

Our findings demonstrate a strong association between reports of traumatic events and certain psychiatric disorders. In other studies, negative experiences were reported by individuals with diagnoses such as affective disorders (Bernet & Stein, 1999; Gladstone et al., 1999) and schizophrenic disorders (Cullberg, 2003; Read & Ross, 2003), but these experiences were less common and cumulatively less severe. Negative experiences were particularly prominent in patients with personality disorders (Paris, 1997; Shearer et al., 1990; Zanarini et al., 2002) and in patients with substance-related disorders (Brown & Anderson, 1991; Ellason, Ross, Sainton, & Mayran, 1996; Windle et al., 1995). Negative experiences were reported more often in late childhood and adolescence than in early childhood and adulthood. Previous studies indicated that the earlier onset of abuse was associated with greater severity and longer duration of mental problems (Briere & Zaidi, 1989; Brown & Anderson, 1991; Fergusson, Horwood, & Lynskey, 1996; Read, 1998).

If the present findings are consistent with some prior studies (Mullen et al., 1993; Palmer, 1992; Wurr & Partridge, 1996) in that they indicate a relationship between physical and sexual abuse and psychiatric disorders, they do not support the view expressed by Van der Kolk et al. about early abuse at an early stage of development (B. A. van der Kolk, Hostetler, Herron, & Fisler, 1994). The current investigation showed that many psychiatric patients had terrible histories of childhood physical and/or sexual abuse. This finding was marginally significant for the childhood sexual abuse histories and must therefore be interpreted with caution. However, one should keep in mind that self-report questionnaires depend heavily upon conscious retrieval capacity for autobiographic events. It is conceivable that in the current group of patients, early abuse events were less remembered as compared to abuse events experienced later in childhood. An advantage of the TAQ used in the present study is the assessment of negative experiences during both childhood and adulthood, while most of the other studies have so far focused primarily on the impact of childhood abuse, except Cascardi et al. (Cascardi et al., 1996) and Goodman et al. (Goodman et al., 1997). Another advantage of the TAQ is that it addresses the issue of neglect (Cohen, Brown, & Smaile, 2001). Given the sample of patients with different psychiatric diagnoses, this replicates Van der Kolk´s et al. notion that patients who experience neglect early in their lives develop serious problems with affect regulation (B. A. van der Kolk & Fisler, 1994). The present data add to the evidence, suggesting that neglect, emotional and physical abuse are experienced by many psychiatric patients (Bierer et al., 2003; Muenzenmaier et al., 1993). This implies that although childhood traumas may contribute to a mental disorder in adulthood, the lack of secure attachments maintains it. Although emotional neglect has received less attention, perceived emotional rejection by parents has been associated with alcohol abuse (Campo & Rohner, 1992) and delinquency (Haapasalo & Hamalainen, 1996) during adolescence and adulthood. Early emotional injuries could possibly trigger vulnerability to noxious experiences.

Furthermore, experiences of parental loss or separation were prominent in adulthood especially for the patients with alcohol-related disorders and with affective disorders. The high incidence of such negative experiences during this period in the patients with alcohol-related disorders could be, at the same time, a direct consequence of the behavioral deviance of these individuals and contribute to the maintenance of alcohol abuse.

Limitations of the study

The present data has to be considered in the light of several possible limitations. First, the information obtained by self-report and without external evidence could be less reliable and valid, especially if we take into account the sensitive nature of this research. Herman and Schatzow, however, provide empirical support for the validity of abused patients' self-reports as well (Herman & Schatzow, 1987). They found that when corroborating evidence is sought, the majority of women are able to obtain confirmation of abuse. No independent corroborating evidence was sought for any self-reported case of childhood negative experiences. Therefore, the validity of abuse reports cannot be assured. Recall may be biased, but there is no evidence that psychiatric patients are more likely to lie about or imagine child abuse (Goodman et al., 1999; Margo & McLees, 1991). There is some evidence, however, that "patients are biased to underreport abuse histories rather than to over report them" (Dill, Chu, Grob, & Eisen, 1991). There were some "don't know" subject answers regarding abuse/neglect experiences, most of them in the early childhood. Most probably, the patients had difficulties recalling experiences that occurred at a very young age rather than trying to evade giving a positive answer. Furthermore, another methodological limitation in this study is that measuring neglect/emotional abuse in early childhood is particularly difficult as the awareness of it necessitates the development of a degree of differentiation and autonomy, which is seldom the case with psychiatric patients.

Both individual interviews and self-report questionnaire methods present higher figures than chart reviews do, indicating that patients usually do not spontaneously offer such information to their therapists. When offered, the information is not reliably documented (Margo & McLees, 1991). However, the data from our ongoing study in patients with personality disorders suggest that reports on events in general and physical abuse events in particular are highly stable across two measurement periods of time separated by 24 months. We also note that our sample consisted of psychiatric inpatients, and thus may not be representative of the broader population of patients with these disorders. The clinical validity of the TAQ has also been criticized (B. van der Kolk). The questionnaire is meant to be an applied clinically oriented measure, which has not yet been proved to be a psychometrically sound research instrument. This issue should be addressed in future studies using both convergent and divergent instruments.

Romanian patients diagnosed with schizophrenic disorders differed significantly, with respect to the number of negative events, as compared to their German counterparts. One factor accounting for this difference might be the stressful environment during the former Ceausescu regime in Romania. During this 25-year period violations of human rights, terror, and corruption prevailed (Loue, 2002; Stefanis & Reisby, 1993). This result may also be due to the different diagnostic procedures used by Romanian and German/Swiss clinicians. Reports of higher rates of psychotic-like or specifically schizophrenic symptoms do not necessarily imply a diagnosis of schizophrenia. Once abuse is identified, a change of diagnosis, from schizophrenia to PTSD, is often made, with significant advantages for the individuals (Read, 1997).

Conclusions

The present study demonstrates an association between negative life events in childhood and psychiatric diagnoses in adult life, which is in line with a number of other studies (Ellason & Ross, 1997; Mulder et al., 1998). Unlike previous reports (Coverdale & Turbott, 2000; Herman et al., 1989), we found that psychiatric patients were more likely to report more negative life events during late childhood and adolescence rather than during early childhood and adulthood. These conclusions corroborate with one of the central hypothesis of life-span psychotraumatology, that is, adolescence is an extremely critical phase in the development of later psychopathology (Maercker et al., 2004; Schutzwohl & Maercker, 1999). However, in line with findings offered by earlier controlled studies (Palmer et al., 1994; Palmer et al., 1993), psychiatric patients were more likely to report higher rates of negative life events during childhood than controls did.

Although one cannot assume a direct causal relationship between childhood abuse and adult psychopathology from the present data, the present study provides further preliminary and explorative evidence for the high load of negative life events in psychiatric patients. An advantage of this study is the examination of the abuse histories across a range of four psychiatric diagnoses within a controlled comparison design. Our findings are important and clinically highly relevant for further etiological research of causal and maintenance factors of psychiatric symptomatic, as well as for the research on the treatment of these conditions.

The special value of the study lies in its cross-national comparison from a clinical psychological point of view including a highly underresearched country like Romania. More attention should be paid to the sad situation of the patients in Romania who are often under inadequate pharmacological and insufficient psychotherapeutic treatment, as well as under inappropriate hospitalization conditions. Further research should concentrate on the epidemiology and developmental psychopathology of psychiatric populations in other countries than the usually researched ones. Generally, reports of traumatic experiences during the whole lifespan should be more carefully considered in the clinical diagnosis process and in the development of treatment programs for the psychiatric patients.

Chapter 3

[1]Study II

MEG correlates and heart rate modulation during affective picture processing in PTSD: evidence from magnetoencephalography (MEG)

3.1 Summary

PTSD is marked by nightmares, flashbacks and intrusive memories of traumatic events. In PTSD subjects, exposure to trauma-related stimuli is associated with subjective experiences of anxiety (self-reported distress), physiologic reactivity (e.g. changes in heart rate), and widespread activation in the human cortex. In our study, we implemented a visual paradigm to investigate cortical activation patterns during processing of high arousing (pleasant and unpleasant) as compared to low (neutral) arousing pictures in PTSD. In addition to magnetocortical data we examined subjective ratings, heart rate and startle responses in 15 PTSD patients, 15 schizophrenia inpatients and 12 healthy control participants. PTSD patients showed a differential sensitivity for the early time windows for high arousing pictures. Avoidance symptoms in PTSD patients were negatively correlated with the difference unpleasant minus neutral for the N1m time window suggesting that amplified responses for neutral pictures were negatively correlated with high avoidance scores. PTSD patients showed for the late components increased activity for high arousing pictures suggesting cortical facilitation in attentional processes. Heart rate responses differed significantly among PTSD patients, schizophrenia patients and control participants showing sustained heart rate acceleration for high arousing unpleasant pictures in PTSD patients. Taken together, the earlier amplification for neutral pictures in PTSD patients such as found in the range of the N1m component may indicate initial cortical inhibition of magnetic fields for visual features

[1] Studies II and III are based on the same sample of participants.

that are motivationally significant may be associated with PTSD symptoms. In addition, increase in physiological reactivity including heart rate responses in PTSD patients suggests that these peripheral markers may be related with activation in higher order cortical networks.

Keywords: PTSD, Emotion, Magnetoencephalography, visual paradigm, heart rate change

3.2 Introduction

Posttraumatic stress disorder (PTSD) is a psychiatric condition that may develop following the experience of an overwhelmingly traumatic event (i.e., combat, torture, assault, sexual abuse). PTSD is characterized by nightmares, flashbacks, intrusive recollections of traumatic events, increased fear responding, increased startle (American Psychiatric Association 1994) and other symptoms that can persist for many years after the original traumatic event (Bremner, Krystal, Southwick, & Charney, 1995; Pitman, Orr, Shalev, Metzger, & Mellman, 1999). PTSD has been associated with several different types of traumatic events, including combat experience (Prigerson, Maciejewski, & Rosenheck, 2001), torture (Basoglu et al., 1994) and sexual assault (Foa, 1997). In PTSD subjects, exposure to trauma-related stimuli is associated with subjective experiences of anxiety (self-reported distress), physiologic reactivity (e.g. changes in heart rate) (E. B. Blanchard, Kolb, & Prins, 1991; Buckley & Kaloupek, 2001; Orr, Meyerhoff, Edwards, & Pitman, 1998), and widespread activation in the human cortex (Lewine et al., 2002) (Attias, Bleich, Furman et al., 1996; Kimble, Kaloupek, Kaufman, & Deldin, 2000; Kounios et al., 1997). Several studies suggest that PTSD subjects produce distinctive physiologic changes to a variety of different stimulus types (Kimble et al., 2000; Shalev, Orr, & Pitman, 1993; Shalev & Rogel-Fuchs, 1993). PTSD subjects exposed to simulated combat noise, and individualized scripts depicting stressful combat experiences, or to imagery of traumatic events induced by hypnosis, showed increased physiological responses as compared to combat veterans without PTSD (Orr, 1997; Orr, Pitman, Lasko, & Herz, 1993; Pitman et al., 1987). All those studies only used peripheral physiological markers. The implication of conditioning theory in PTSD, a defined behavioral model of emotional learning and memory processes, have helped elucidate in great detail the neural circuitry underlying fear conditioning (Armony & LeDoux, 1997; LeDoux, 1995). Southwick et al (1994)(Southwick, Bremner, Krystal, & Charney, 1994) reported that conditioning mechanisms can produce fear and anxiety in response to a variety of external stimuli in subjects with PTSD. Taken together, the most work on the neurobiology of PTSD has focused on characterization of abnormal psychophysiological correlates to stimuli reminiscent of the traumatic event (Bremner, Staib et al., 1999; Lewine et al., 2002; Liberzon et al., 1999).

Within the past decade, there has been a notable increase in the application of event related potentials (ERP's) to examine neurophysiological events associated with information processing abnormalities in PTSD. To date, recent electrophysiological research suggests abnormal conscious processing in the evaluation of stimuli in PTSD subjects (Blomhoff et al., 1998; Bremner, Staib et al., 1999; Gerhards, Yehuda, Shoham, & Hellhammer, 1997; Kimble et al., 2000; Lewine et al., 2002). The psycho-physiological relationship between traumatic stimuli and physiological hyperactivity in PTSD subjects suggests a specific cognitive response to traumatic stimuli (Bleich, Attias, & Furman, 1996; Kimble et al., 2000). ERP studies that use neutral stimuli (e.g. auditory tones) have revealed abnormalities on measures of early processing (mismatch negativity, P50) suggestive of PTSD –related deficits in sensory gating (Morgan & Grillon, 1999; Neylan et al., 1999) and later components (e.g. P2, P3) thought to reflect cognitive processing (Charles et al., 1995; McFarlane et al., 1993). In general, PTSD diagnosis has been associated with reduced P3 amplitudes and delayed latencies in response to neutral target stimuli. Consistent with descriptive neuropsychological studies suggesting that PTSD-related deficits on tasks of attention and working memory, findings of attenuated physiological reactions among PTSD-diagnosed trauma victims have been attributed to deficits in attention modulation and memory update (Vasterling et al., 2002).

The use of event-related magnetic fields (ERF's) and event-related potentials (ERP's) provides ways of testing theories of abnormal brain functioning that no other method can offer (Elbert, 1998). ERP's are the reflections of patterned neural activity associated with information processing in the brain (Attias, Bleich, Furman et al., 1996; Attias, Bleich, & Gilat, 1996). More recent studies examining ERP's in PTSD have shown that stimulus relevance may affect electrophysiological response.

Paige, Reid, Allen & Newton (Paige et al., 1990) studied the P2 ERP component in response to four intensities of tones presented in an augmentation/reduction paradigm. PTSD subjects exhibited reduced P2 amplitudes in response to an increase in pure tone intensity (reducers), while controls showed augmented P2 amplitudes (augmenters). The authors attributed these finding to the activation of a protective inhibition mechanism in PTSD patients, probably due to the continuous sensation of exposure to threatening stimuli. In another study, Lewine et al (Lewine et al., 1997) sought to replicate and extent the work by Paige et al (Paige et al., 1990) by combining EEG measurements with magnetoencephalographic (MEG) measurements. Control subjects demonstrated an augmentation pattern in which louder sounds elicited larger responses. Less than the half of the PTSD subjects showed this pattern. Some subjects showed poor auditory responses and half of them showed a reducing pattern in which the response to the loudest sound was smaller than that to intermediate sounds. This, combined with the MEG localization of the P200 response to auditory association cortex, indicates that the reducing effect reflects a decrease in the activation of the auditory association cortex.

In contrast to Paige et al (1990), one study has used ERP's to investigate how PTSD patients process stimuli that are not specifically trauma-related (McFarlane et al., 1993). In an auditory oddball paradigm, where tones were used as stimuli, PTSD patients showed delayed

N200 latency and smaller P300 amplitude to both certain stimuli (targets) and other stimuli (non-targets). P3 was found to be delayed and attenuated in PTSD patients. The authors attributed these findings to impaired evaluation of stimuli in PTSD patients. Further, the authors suggested that this information processing dysfunction might be the cause of concentration and memory difficulties, often observed in PTSD patients. If this is so, much of the PTSD phenomenology maybe related to abnormal attentional processing (Blomhoff et al., 1998). The variety of stimuli that elicit psycho-physiological reactions in PTSD thus may have their effect through their cognitively based association with the traumatic event, or even, with the emotions elicited by the traumatic event. Based on this observation, one study has used words with varying emotional content in an ERP paradigm (Blomhoff et al., 1998).

In another study, Attias et al (1996) used visual stimuli to examine the ERP patterns in Israeli combat veterans consisting of PTSD sufferers and normal controls. ERP's were recorded in response of visual stimuli presented in the form of a modified oddball paradigm. Subjects were asked to press a button when target stimuli (domestic animal pictures) appeared, and to ignore all the non-targets stimuli (emotionally neutral pictures of furnishings and combat-related pictures (non-targets). Target stimuli evoked accentuated P3 amplitudes in both control and in PTSD patients. The non-target combat -related pictures elicited enhanced P3 and N1 amplitudes in the PTSD patients. The authors suggested that these results might indicate that an altered state of early and late cognitive selective attention processing existed in PTSD patients (Attias, Bleich, Furman et al., 1996). Similarly, Bleich et al (1996) examined P3 changes in response to repeated traumatic pictorial stimuli in the form of a visual discrimination oddball paradigm (Bleich et al., 1996), as did Attias et al (1996) with a paradigm that used targets (domestic animal pictures) and non-targets (irrelevant pictures of furnishings/flowers and traumatic combat related pictures). On average, P3 in response to non-targets (combat related pictures) was earlier and approximately five times greater in amplitude for the PTSD patients as compared to the controls. These results suggest that a gradually reduced amount of attentional capacity is required and allocated to the processing of repeated combat related pictures stimuli.

Looking at pictures with emotional content has been found to be a powerful tool to activate brain structures involved in emotion processing. In neurophysiological studies, emotionally charged pictures have been proven to evoke a spectrum of measurable emotional reactions (Bauer, 1998; Bradley, Cuthbert, & Lang, 1996; P. J. Lang, Bradley et al., 1998a, 1998b). Emotionally laden pictures were successfully used to activate emotion-related brain regions, as well (H. D. Critchley et al., 2000; R. A. Davidson, Fedio, Smith, Aureille, & Martin, 1992; Hariri et al., 2003; Paradiso et al., 1997; Schneider et al., 1999; Whalen, Rauch et al., 1998; Wright et al., 2001). As one possible laboratory paradigm of emotional processing, viewing of emotional pictures has been shown to co-vary with measures indicative of the motivational state of the organism. The perceptual processing of pictures, in terms of the degree of attentive engagement, is presumed to be determined in considerable part by their motivational significance (Cuthbert et al., 2000). In particular, pleasant affects are considered to be associated with the brain's appetitive motivation system while unpleasant affects are considered to be associated with the defensive motivation.

The present study uses an approach that has recently been shown to invoke a reliable measure of affective valence in healthy subjects. According to Lang (P. J. Lang, 1985) this approach is associated with a two-dimensional (2D) model of emotion: affective valence and arousal. The valence refers to the direction of behavioral activation associated with emotion, either toward (appetitive motivation, pleasant emotion) or away from (aversive motivation, unpleasant emotion) a stimulus. Arousal is proposed to be orthogonal to valence and refers to the intensity of emotional activation, ranging from excited to calm. The valence dimension is related to variations on the level of the two motive systems, i.e. 'appetitive' versus 'aversive' and this is connected to an action disposition organizing behavior along avoidance –approach dimension. The arousal dimension adds to the 2D affective space a component that modulates the emotional behavior regarding to activation or intensity (P. J. Lang, Bradley et al., 1998b). To date, noninvasive functional neuroimaging have given us the tools to explore brain mechanisms underlying the unconscious physiologic responses to arousing stimuli (Hariri et al., 2003; P. J. Lang, Bradley, Fitzsimmons et al., 1998; Rauch et al., 2000; Schneider et al., 1999; Wik et al., 1993).

The purpose of the current MEG study was to investigate magnetic cortical activation patterns during visual emotional stimulation in torture victims and survivors of organized violence with PTSD, relative to schizophrenic patients and to healthy control participants. MEG is a non-invasive technique for investigating neural activity in the living brain. In MEG studies, the weak magnetic fields produced by electric currents flowing in neurons are measured with multichannel SQUID (Superconducting Quantum Interference Device) magnetometers. The sites in the cerebral cortex activated by a stimulus can be calculated from the detected magnetic field distribution.

In the present study we used the International Standardized Affective Picture System (IAPS) (P. J. Lang, Bradley, M.M., Cuthbert, B.N., 1999), which provides a large data set of standardized pictures. We hypothesized that PTSD subjects respond in a different manner to pictures of the IAPS as compared to the way affectively disturbed patients or healthy controls do. We hypothesized that PTSD patients would display an enhanced fear potentiation at a very early stage of visual processing (P. J. Lang, Bradley et al., 1998b). We expected therefore that PTSD subjects would exhibit a specific enhancement of the magnetic field in response to high arousing stimuli. PTSD subjects who have a persisting conditioned emotional response (startle reaction) to stimuli reminiscent of the traumatic event would demonstrate different magneto-cortical activity measured in the context of emotional stimulation. We hypothesized therefore that emotional traumatic experience in PTSD patients could modify visual processing already at the pre-attentive level. In identifying the response patterns of evoked magnetic fields during emotional processing of the IAPS, autonomic responses (measured by changes in heart rate-HR) were registered simultaneously to validate the effectiveness of the stimuli and to investigate the relationship between MEG responses and HR responses during picture processing. An open question is whether brain responses to emotionally laden stimuli can influence cardiac autonomic responses in response to the same material. Answering this question is important because the brain's regulation of cardiac autonomic activity is supposed to influence a range of behavioral processes such as attending to novel stimuli (Porges, 1995), experiencing fear and anxiety (Berntson, Sarter, & Cacioppo, 1998), reacting to stressors (Lovallo & Gerin, 2003), are examples of such processes. Considerable evidence has accumulated, however, indicating a range of visceral influences on higher neurobehavioral processes (Gianaros, Van Der Veen, & Jennings, 2004). Lane et al. (2001) used positron emission tomography to examine the relationships between regional cerebral blood flow (rCBF) and high-frequence heart period variability (HF-HPV) in participants who viewed emotional films and recalled emotional experiences. The authors reported that during these emotional tasks, increased rCBF in medial prefrontal and insular cortical regions correlated with increased HF-HPV. Other studies have failed, however, to find statistically significant correlations between rCBF and HF-HPV associated with performance of a stressful mental arithmetic task (Shapiro et al., 2000).

To our knowledge this is the first MEG study which examines the relation between magneto-encephalographic and cardiovascular responses. Correlations of functional MRI (fMRI) responses and HR responses have been described in the literature (Wagner et al., 2001). Very few human functional neuroimaging studies (Berntson, Sarter, & Cacioppo, 2003; Gianaros et al., 2004) have investigated whether and how measures of cortical activity relate to measures of cardiac autonomic activity during cognitive or emotional behaviors. Palomba et al. (Palomba et al., 1997) in a study with visual evoked potentials found a correlation between the Slow Negative Wave (600-900 ms epoch), at Cz, and heart rate changes: subjects who showed higher cortical excitability also exhibited higher heart rate deceleration. Nevertheless, such a correlation in torture victims and survivors of organized violence with PTSD has not yet been demonstrated, and little is known about how and if cortical responses to emotional laden pictures (systems) co-vary with HR responses. Moreover, based on human and non-human animal research we expected that changes in HR responses would correlate with cortical responses during emotional picture processing.

In the present study, additional physiological (startle reflex) and subjective measures (of valence and intensity of the emotional experience) were recorded. Affective modulation of the startle reflex has been demonstrated using picture durations ranging from brief (150 ms) to relatively long (6 s) durations. In addition, the affective modulation of the startle reflex appears very rapidly after picture onset (within 300 ms) (Codispoti, Bradley, & Lang, 2001). The magnitude of the startle eyeblink response has been shown to be sensitive to the valence of affective stimuli (Bradley & Lang, 2000). Individuals show increased startle magnitude when presented with negatively valenced or aversive stimuli and decreased eye-blink magnitude when presented with positive or appetitive stimuli; the magnitude of the resultant eye-blink is largest for aversive pictures and smallest for attractive picture content (Vrana et al., 1988).

3.3 Methods and Materials

3.3.1 Subjects

Thirty patients who were referred for evaluation at the Psycho-trauma research clinic, an outpatient clinic for refugees located at the Center for Psychiatry Reichenau and, and 12 healthy volunteers were included in the present study. The patient sample included 15 torture victims and survivors of organized violence with a current diagnosis of PTSD and 15 schizophrenic inpatients of the Center for Psychiatry Reichenau. Because of movement artifacts, three participants from the experimental group of torture victims and survivors of organized violence, 3 participants from the clinical control group of schizophrenia inpatients and 2 participants from the group of healthy participants, had to be excluded. All subjects were right handed (Oldfield, 1971). At the end twelve torture victims and survivors of organized violence (2 women, 10 men; mean age 26.9 years ± 6.09), twelve schizophrenia inpatients (4 women and 8 men; mean age 29.08 years ± 8.7) and ten healthy subjects (5 women and 5 men; mean age 25.1 years ± 6.4) participated in the study.

At the time of testing all patients with schizophrenia were receiving treatment with typical anti-psychotics only (the mean chlorpromazine equivalent was 128.36 mg/day [± 83.3, range 0 to 400]. Two inpatients were additionally receiving antidepressants. Five patients were being treated with antianxolytic medications (benzodiazepines) including buspirone, clorazepate and diazepam. Two of these patients were being treated with antidepressants, including amitryptilin and paroxetin. All of them were receiving analgesic medications including paracetamol and metamizol.

Written informed consent was obtained from all subjects, and all procedures were conducted as approved by the local University Ethics Committee. Magnetoencephalography (MEG) was performed at the psycho-physiological laboratory at the center for Psychiatry in Reichenau.

3.3.2 Clinical Ratings

Torture victims and survivors of organized violence met the criteria for current PTSD as assessed by the Post-Traumatic Diagnostic Scale (PDS) (Foa, 1995; German translation by Ehlers, Steil and Winter, 1996). The PDS is a 49-item self-report instrument designed to aid in the detection and diagnosis of PTSD. The PDS has been demonstrated to be a reliable and valid measure in the assessment of PTSD symptom severity and functioning in patients identified as suffering from PTSD (Brewin et al., 2002). The PDS is based on the DSM-IV (American Psychiatric Association, 1994) diagnostic criteria for PTSD. Subjects were classified as meeting Criterion A for PTSD if they reported the occurrence at least one major life event at some time during their lives. A positive current PTSD diagnosis was assigned if the respondent met DSM-IV criteria by having the necessary number of PTSD Criterion B (one re-experiencing), criterion C (three avoidance), Criterion D (two arousal), Criterion E (duration of the symptoms; acute when symptoms have been present for less than three months, chronic: when symptoms have lasted three months or longer, and with delayed onset: when symptoms onset occurred at least six months after the traumatic event) and Criterion F (level of impairment in functioning, at least one). At our study we used the PDS as a clinical screening taking into account the educational level in torture victims and survivors of organized violence with PTSD. For the assessment of political history and torture experience a modified version of the Semi-structured Interview for Survivors of Torture (Keane, Scott, Chavoya, Lamparski, & Fairbank, 1985) was used, based in part on the Basoglu interview form (Basoglu et al., 1994). This interview consists of two parts: 1) demographic details, personal history, forensic history (political), history of political activity, non-torture stress factors before, during and after detention/imprisonment, and post-trauma adjustment, and 2) a checklist of forms of torture, the number and duration of exposures. To assess symptoms of anxiety and depression the Hopkins Symptom Checklist-25 (HSCL-25, German translation)(Derogatis, Lipman, Rickels, Uhlenhuth, & Covi, 1974; Hesbacher, Rickels, Morris, Newman, & Rosenfeld, 1980; Rickels, Garcia, Lipman, Derogatis, & Fisher, 1976; Winokur, Winokur, Rickels, & Cox, 1984) was administered. The HSCL-25 uses 10 items from the HSCL-58 anxiety cluster and 13 items from the depression cluster. It also includes two additional somatic symptoms. Scores on the HSCL-25 were determined for three categories: total, depression, and anxiety. The total score is the sum of all the scores of the items answered divided by the number of items answered (25); the anxiety score equals the sum of the first 10 item scores divided by 10; the depression score equals the sum of items 11-25 divided by 15. Subjects with scores higher than 1.75 on the total score, anxiety score, or depression score were classified as having significant emotional distress (Mollica, Wyshak, de

Marneffe, Khuon, & Lavelle, 1987). Somatoform and dissociative (conversion) disorders were assessed using the German versions of DSM-IV adapted Composite International diagnostic Interview (CIDI) part C, a structured diagnostic interview. The CIDI-C module was used to measure somatization symptoms. It consists of 39 questions a series fixed coding options, and a clearly specified probing system that allows the interviewer to determine the severity and likely psychiatric significance of a positive symptom. The minimum number of separate complaints that have to occur in order to qualify for this disorder is eight, including 4 pain symptoms, 2 gastrointestinal symptoms, 1 sexual symptom, and 1 pseudo-neurological symptom. Some subjects in the PTSD group met the criteria for the following current comorbid diagnoses: major depression (n = 3).

Schizophrenia inpatients served as a clinical control group, fulfilling the DSM-IV criteria for schizophrenia. Schizophrenia inpatients were evaluated by psychologists on four different rating scales: the German version of the Positive and Negative Syndrome Scale (PANNS) (Kay, Fiszbein, & Opler, 1987), the German version of the Calgary Depression Scale for Schizophrenia (CDSS) (Addington, Addington, & Maticka-Tyndale, 1993) and the German version of the Schedule for the Deficit Syndrome (SDS) in schizophrenia (Kirkpatrick, Buchanan, McKenney, Alphs, & Carpenter, 1989).

A group of ten healthy participants served as controls consisting of five subjects matched to the PTSD group on mean age and sex, and five subjects who were matched to the group of schizophrenia inpatients, on the same criteria. Control participants were administered the PDS for the assessment of PTSD and the HSCL-25 for the assessment of levels of anxiety and depression. Control subjects did not meet Criterion A for PTSD (and consequently the criteria for PTSD). The presence of other psychiatric disorders was assessed with the Structured Clinical Interview for DSM-IV (First et al, 1995). None of the control subjects had current diagnoses and none of the control subjects had a history of psychiatric disease.

Mean age was 26.9 ± 6.09 years for the PTSD group, 29.08 ± 8.7 years for the schizophrenia group, 25.1 ± 6.4 years for the normal control group. Differences between the each of the patient and the control group did not reach significance ($p > .5$). Additionally, groups did not differ significantly regarding on sex ($\chi^2 = 2.7$, $p = .25$) (Table 3.1). All subjects were free of metallic implants, neurologic and major medical conditions, and cardiovascular medications.

3.3.3 Stimulus Material

Visual

Thirty six pictures were selected form the IAPS (Center for the Study of Emotion and Attention, 1999) consisting of 12 pleasant, 12 neutral, and 12 unpleasant pictures, based on pleasure and arousal ratings. Highly arousing pleasant pictures included erotic couples and happy families; low arousing neutral pictures included neutral faces and household objects; high arousing unpleasant pictures included mutilated bodies, an aimed gun and scenes of attack and threat. Pleasant and unpleasant pictures were selected to be the most arousing exemplars in the respective subcategory. Mean (±SEM) normative ratings of valence on a 9-point scale for pleasant, neutral, and unpleasant, where 1 represents maximum negative and 9 maximum positive were 7.1 (± 0.72), 4.9 (± 0.32) and 2.6 (± 0.57), while mean normative arousal ratings were 5.0 (± 1.09), 3.4 (± 0.74) and 6.0 (± 1.08), respectively, based on previous data from large samples of healthy volunteers (Lang, 1997). Brightness, contrast and color spectra of the stimuli were adjusted so that there were no systematic differences between picture categories in regard to these parameters.

Acoustic probe

The acoustic startle eliciting-stimulus was a 50-ms white noise burst presented at 95 dB SPL [A] with instantaneous rise time. Startle probes were presented binaurally through hollow plastic tubes.

3.3.4 Procedure and Experimental Paradigm

After arriving at the laboratory, all subjects were allowed a period of adaptation to the recording environment to maximize cooperation and minimize psychological discomfort to the novel situation. Afterwards, they were prepared for the MEG recording conducted using a whole-head neuromagnetometer system. After giving informed consent, handedness was determined using the Edinburgh Inventory (Oldfield, 1971). To monitor eye movements and blinks, the electrooculogram (EOG) was measured, with four electrodes attached, two at the left and right outer canthus and two above and below the right eye. A ground electrode was attached behind the right ear. In addition, two electrodes for the electrocardiogram (ECG) were placed on the left and right medial forearms. For the eye-blink component of the acoustic startle reflex, electromyographic (EMG) activity was recorded from the orbicularis occuli muscle beneath the left eye (the first electrode beside the canthus and the second located 1 cm to the right of the first, below the eye (P. J. Lang et al., 1990).

The location estimates of each 'dipolar activity' source were specified with reference to a Cartesian coordinate system, as follows. Subjects, were seated in the MEG chamber and the position of the magnetometer sensor with respect to the center of the head was determined at the beginning of each recording session by registering the magnetic fields produced by currents fed into five circular coils: three coils attached to the subject's forehead and to the left and right pre-auricular points. Head position was measured before and after each recording session to ensure that the head remained stable throughout the recording. The relative location of these coils was digitally recorded before placing the head into the magnetometer sensor using an Isotrak 3D-digitizer (Polhemus™, USA).

Subjects were told that a series of pictures would be presented and that each picture should be viewed the entire time it was exposed on the ceiling. Subsequently, participants were told that a fixation point would appear before the presentation of each picture and that it would be present throughout the experiment. All pictures were centered on the fixation point. In addition, subjects were told that at various times during the experiment they would hear a loud noise through their earphones, which should be ignored. To this end, subjects were instructed to maintain gaze on the fixation point and to avoid exploratory eye movements and eye blinks during picture presentation. Lastly, participants were lying comfortably in a dimly lit, magnetically shielded room (Vacuumschmelze GmbH, Hanau).

During the recordings, the stimuli were delivered inside the magnetically shielded room via a video projector (JVC™, DLA-G11E) located outside of the room and a system of mirrors. Pictures were finally projected on the ceiling of the shielded room at approximately 120 cm above the participants' eyes.

Presentation and startle stimuli were under control of the Software Experimental Run Time System, Version 3.18 (ERTS; Beringer, 1996) installed on an IBM™ compatible personal computer.

Experimental Paradigm

The experiment started with the presentation of pictures in a pseudo-randomized order. Randomization was restricted, so that no more than three pictures in the same affective category could occur in a row. The experiment included three blocks (runs), each consisting of the same 60 trials. In each trial, a single cross that served as a fixation point was presented for 500 ms, than a picture was presented for a period of 2000 ms. During the inter-trial interval (ITI), which varied randomly between 4000 ms and 10000 ms, a black screen was presented. The acoustic startle probe was presented for 50 ms during picture presentation, with a stimulus onset asynchrony varying between 1000 and 1850 ms after picture onset (Figure 3.1). Additional startle probes were presented randomly during picture presentation. The viewing time prior to the probe was counterbalanced across slide types.

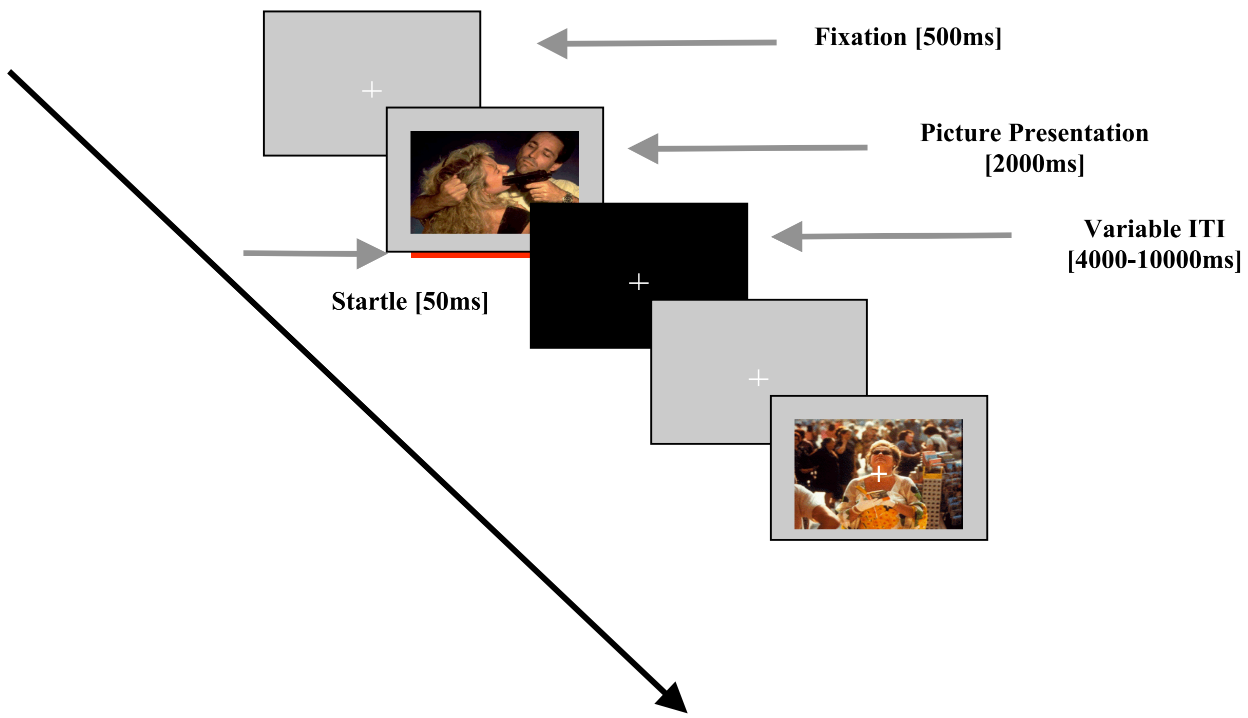

Figure 3.1: Graphical representation of one trial.

After the first block subjects were offered a brief pause, and a second block of the same 36 pictures in a different order was presented. At the end of the second block the block sequence was repeated. Then, at the end of the MEG session, subjects left the MEG chamber and electrodes were removed.

Immediately after the MEG recordings, subjects viewed some of the pictures again in a pseudo-randomized order and were asked to rate each picture for pleasure and arousal using the paper and pencil version of the Self-Assessment Manikin (SAM) (P. J. Lang, Bradley et al., 1993; P. J. Lang, Greenwald, Bradley, & Hamm, 1993). SAM is a language-free instrument for rating pleasure and arousal, and consists of a graphic figure representing nine levels each of pleasure and arousal. The levels ranged from 1 (very unpleasant) to 9 (very pleasant) for ratings of emotional valence and from 1 (not at all) to 9 (very strong) for ratings of emotional arousal, with 5 representing a neutral rating in both dimensions.

3.3.5 MEG Recording and Data analysis

MEG data were recorded with a whole-head neuro-magnetometer (MAGNES^{TM} 2500 WH, 4D Neuroimage, San Diego, USA) that consisted of 148 axial magnetometer coils placed in a cryogenic container. The EOG, EMG and ECG acquisition was done with a SynAmps amplifier (NEUROSCAN^{TM}) using Ag/Cl electrodes.

MEG data were acquired with a sampling rate of 678.17 Hz and a band-pass filter of 0.1-200 Hz was applied on line. Raw data were noise-reduced to remove environmental artifacts. Responses exceeding a range of 5 pT in any of the MEG channels were omitted from averaging.

After reduction of external noise, MEG data were digitally filtered using a low-pass filter set at 20 Hz (12 dB/octaves) and then submitted to the procedure proposed by Junghöfer, Elbert, Tucker, and Rockstroh (Statistical Correction of Artifacts in Dense Array Studies, SCADS) (Junghofer, Elbert, Tucker, & Rockstroh, 2000). A 296 ms interval preceding the first stimulus was used for baseline correction. The SCADS procedure uses statistical parameters of the data to exclude channels and trials that are contaminated with artifacts (Keil et al., 2002).

The analysis requires two passes at the data, the first with the data kept in the recording reference, and the second with the data transformed to the average reference. In the case of MEG data (which does not require a reference), the first pass can be omitted, as it will be repeated in the second pass. The term sensor will be used from here on, referring to SQUID sensors in MEG.

In a next step, editing data matrices are constructed to remove or correct sensors that are artifact contaminated. For this matrix, distinct sensors from particular trials are removed based on the distribution of their amplitude, standard deviation, and gradient, which are determined for every epoch. Boundaries have to be determined for each of the three aforementioned parameters (absolute maximum, standard deviation, standard gradient). Selecting the data point in each trial with the largest absolute deviation from zero creates the absolute maxima. All trials with trials above this limit are removed. To identify trials contaminated by artifacts at many or all sensors, a histogram of the distribution, of the artifact-contaminated trials per sensor is constructed. The experimenter determines then a lower boundary for trial rejection. This procedure improves the accuracy of the subsequent sensor epoch interpolation.

Before averaging the remaining trials (i.e., all trials with a sufficient number of intact sensors remaining at this step), epochs that have been identified as artifact-contaminated are replaced by interpolation. In a last step, the standard deviation is computed (for each time point) across all the trials included in the average.

As a measure of global cortical activity and assessment of ERF peaks and their respective time course, we calculated the root-mean-square value (RMS) of the averaged waveforms for a selection of 3 clusters of sensors for each emotional content and for each subject (see Equation 3.1). Before calculating the RMS field strength from the sensors that covered the field pattern of the particular component, the waveforms of each channel at each time point were visually checked. When responses in a certain channel showed drift or the influence of magnetic responses others than the main responses, they were excluded from the analyses. As a result, frontal channels were excluded from the analysis.

Signal power was computed as the square root of the averaged waveforms across selected sensors and for each sample point, where $\boldsymbol{N}$ is the number of sensors and $\boldsymbol{MEG(t)_n}$ the magnetic field strength at some sensor location at time $\boldsymbol{t}$ and trial $\boldsymbol{n}$ (see Equation 3.1).

Selecting sensors of the magnetic field strength for each time point across trials and participants is computed to assess the stability of the averaged waveform.

$$RMS = \sqrt{\frac{1}{N}\sum_{n=1}^{N} MEG(t)_n^2} \quad \textit{Equation 3.1}$$

RMS analysis employing multiple sensors can detect both positive and negative polarities of the magnetic field, and may therefore yield a more accurate measure of latency than that provided by a single sensor (Embick, Hackl, Schaeffer, Kelepir, & Marantz, 2001). The same selection of sensors was held constant for all subjects and for all stimulus categories.

For statistical analysis, the RMS of the magnetic field was calculated for each sample point from a set of selected sensor clusters over each hemisphere. Sensors were chosen on the basis of their showing large responses in the time windows and regions of interest. Four primary peaks were found at approximately 150 ms, 220 ms, 300 ms and 350 ms after picture onset. Mean magnetic field strength at some sensor location at each time point and trial were assessed in the following four time windows, corresponding roughly to N1m (140–220 ms), P2m (220–250 ms), the early P3m (250–340 ms), and the late P3m (350–490 ms). Fig. 3.2 displays the relative position of the selected clusters for each time window. Time windows were selected on the basis of the grand mean RMS for those segments that contained the most prominent magnetic field peaks.

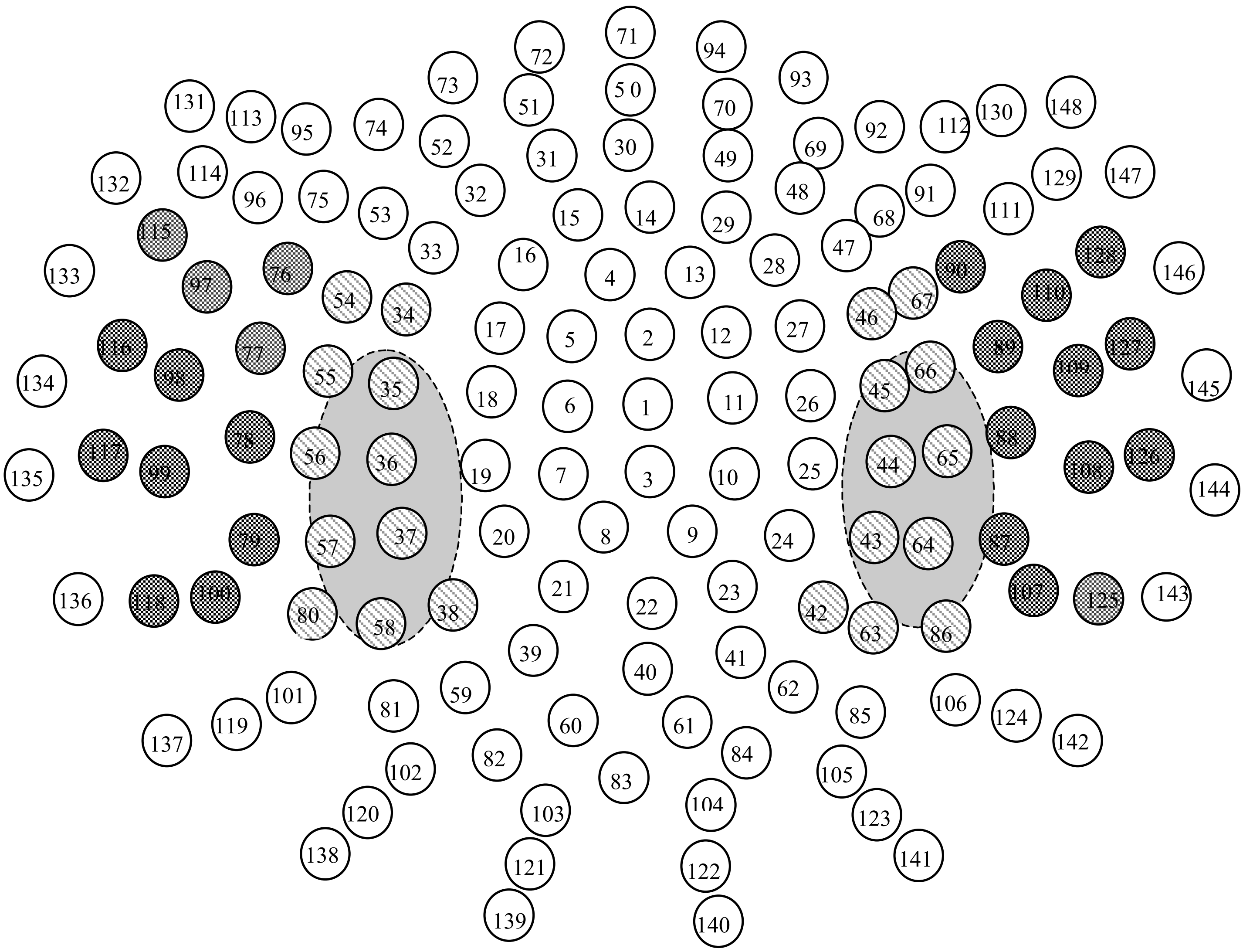

Figure 3.2: Schematic illustration of the MEG sensor layout and the sensor groups with regard to time windows. Sensors in the shaded clusters (N1m, P2m) and encircled sensors (early P3m, late P3m clusters representing: regions used for ANOVAs on RMS).

Changes in heart rate were evaluated using in-house software written in MATLAB™ (Moratti et al., 2004). The algorithm estimated the HR change during picture presentation in 500-ms steps by a 2000-ms prestimulus baseline. Pre-stimulus heart rate was subtracted from the average heart rate for every second following stimulus onset. The frequency of occurrence of an R-wave resulted from the interbeat-interval and weighted according to the distance from a 500-ms step within the time vector. The HR change was transformed in beats per minute (bpm). The heart rate was scored according to a triphasic model of HR change over time (Hare & Blevings, 1975; Hodes, Cook, & Lang, 1985). The minimum bpm value during the first 0.5s after stimulus onset was scored as the initial deceleration, the maximum value within the next 0.5s - window was considered as the ensuing acceleration. Finally, the minimum bpm value in the last 0.5s subsequent to the acceleration was considered as the final deceleration (Figure 3.7).

Amplitudes (in μV) of the startle response magnitudes were determined using in-house software written in MATLAB™. Startle responses were manually scored off-line computing the magnitude of probe-elicited blink in the vertical EOG (Schupp, Cuthbert, Bradley, Birbaumer, & Lang, 1997).

3.3.6 Statistical Data Analysis

3.3.6.1 Demographic Characteristics

Comparisons for demographic and diagnostic data were made with two-tailed unpaired t-tests for continuous variables, and with chi-square tests for discrete variables. Table 3.1 presents the mean (± SD) demographic data for the groups. There were significant group differences with respect to educational level [$F(2,31) = 9.7$, $p<0.005$]. On average, control subjects had more years of education (13.7 ± 5.90 years) than PTSD patients (5.3 ± 5.2 years; $p<0.05$ using the Tukey-Kramer test).

	PTSD patients (n =12)		Schizophrenia patients (n =12)		Control participants (n = 10)		Analysis[2]	
	N	%	N	%	N	%	χ^2	p
Gender							2.7	n.s.
Female	2	5.8	8	23.5	5	14.7		
Male	10	29.4	4	11.7	5	14.7		
	Mean	SD	Mean	SD	Mean	SD	F	p
Age	26.9	6.1	29.1	8.7	25.1	6.4	ns	
Education (yrs.)	5.3	5.2	11.0	2.1	13.7	6.0	10.0	<.0005

Table 3.1: Sociodemographic characteristics of PTSD patients, schizophrenia patients and control participants.

[2] Comparisons of demographic and diagnostic scale data were made with two-tailed unpaired t-tests for continuous variables, or with chi-square tests for discrete variables. Where chi-square values are not shown, p values were determined through binomial distribution

3.3.6.2 Clinical Ratings in torture victims and survivors of organized violence

Approximately half of the 12 patients in the PTSD group were asylum seekers applying for refugee status and the other half had the exceptional leave to remain status. Eleven patients were of Kurdish origin and one was Caucasian. Most came from agricultural or working class backgrounds. Only one torture victim and survivor of organized violence reported 16 years of education. On average, torture victims and survivors of organized violence had spent 54.2 months in exile (SD ± 44.7, range 18 to 153 months) and all of them were living in a residence for refugees. Torture victims and survivors of organized violence had suffered systematic torture during a period of detention [mean number of detention days (9.6 ± 15.8, range 0 to 50 days)]. PTSD patients reported exposure to a mean of 16.4 (SD ± 6.0, range 5 to 26) different forms of torture, including imprisonment (75%), beating (92%), blindfolding (67%), forced standing (58%), restriction of movements (33%), electrical torture (50%), hair pulling (67%), beating of the soles of the feet (falaka) (58%), hanging by wrists (46%), rape (25%), asphyxiation (75%), forced isolation (58%), exposure to extreme temperatures (50%), prevention of personal hygiene (67%), sleep deprivation (67%), deprivation of medical care (92%), lack of food/water (75%), verbal abuse (92%), alternating gentle/rough treatment (42%), threats of further torture (92%), threats of rape (50%), threats of death (92%), threats against family (100%), being striped naked (67%), exposure to sham executions (42%), being made to witness torture (42%), being made to witness rape (9%), being made to witness family member being injured (50%), exposure to combat situation (67%) and hiding from snipers (75%). Table 3.2 shows the distribution of traumatic events experienced by torture victims and survivors of organized violence.

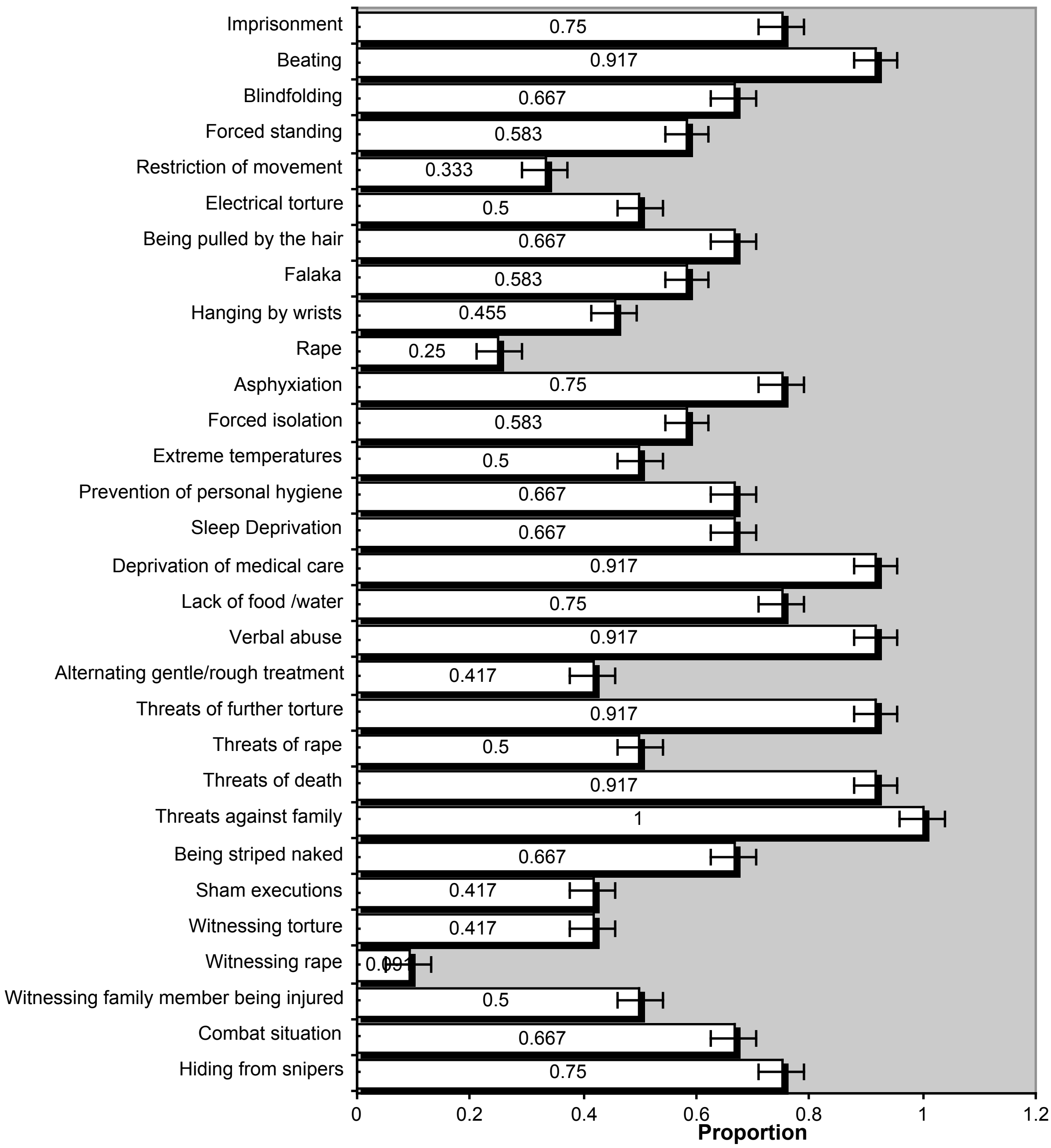

Table 3.2: Forms of torture reported by torture victims and survivors of organized violence.

As expected, PTSD patients reported intrusive (4.6 ± 0.67), arousal (4.5 ± 1), and effortful avoidance symptoms (5.6 ± 1.1), with avoidance symptoms having the highest rates between intrusions [$t(11) = 2.7$, $p < 0.02$] and arousal [$t(11) = 3.0$, $p < 0.01$]. The difference between intrusions and arousal was not significant [$t(11) = 0.4$, $p > 0.7$]. Furthermore, PTSD patients exhibited high scores of emotional distress (3.0 ± 0.42) for both anxiety (3.1 ± 0.55) and depression indices (3.0 ± 0.50) of the HSCL-25 scale. PTSD patients had significantly higher scores than the healthy subjects on both measures of anxiety and depression [emotional distress ($t(20) = 10.0$, $p < 0.001$); anxiety ($t(20) = 7.4$, $p < 0.001$); depression ($t(20) = 9.0$, $p < 0.001$)]. Torture victims and survivors of organized violence reported a high incidence of somatic complaints on the International diagnostic Interview (CIDI) part C. The most frequent scores were observed for pain related complaints [headaches (100%), backpain (33.3%), other pain (42%)] and for pseudo-neurological related complaints [fainting (33.3%), amnesia (42%)]. Despite the fact that many PTSD patients exhibited somatic pain symptoms we did not found any psychiatric significance of a positive symptom.

3.3.6.3 Clinical Ratings in Schizophrenia Inpatients

The average PANSS-P score for schizophrenia inpatients was 15.3 (± 8.0, range 1 to 32), PANNS-N was on average 20.8 (± 6.1, range 14 to 31), mean PANNS-G was 38.4 (± 7.6, range 20 to 54) and mean CDSS was 3.7 (± 2.8, range 0 to 9). With respect to the Schedule for the Deficit Syndrome (SDS) 42% schizophrenia inpatients exhibited moderately severe scores and 58% did not meet the criteria for the deficit syndrome.

3.3.6.4 Inter-correlations among the clinical measures in PTSD patients

We examined further the inter-correlations between the PDS scale and the HSCL-25 scale. Pearson correlations coefficients (r) were performed with B, C, and D symptom subscales from the PDS Scale (which reflect the symptoms of re-experiencing, avoidance, and arousal respectively) with the subscales from the HSCL-25 for the total anxiety scores and the total depression scores.

3.3.6.5 MEG Data Analysis

For the purpose of the statistical analysis grand mean RMS data were computed, in hemisphere-symmetrical clusters located over temporal brain regions. For the N1m left hemisphere channels included 76-79, 97-100, and 115-118, and channels 87-90, 107-110, 125-128 over the right hemisphere. Corresponding channel clusters for P2m included channels 34-38, 54-58, and 76-80 (left), and 42-46, 63-67, and 88-90 (right); and channels 35-38 and 55-58 (left), and 42-45 and 63-66 (right) for the early and late P3m; The same channel clusters were used for all subjects and for all conditions (pleasant, neutral, unpleasant) where these components showed maximal amplitude (Figure 3.2).

Mean magnetic field strength in these selected clusters of sensors was assessed in four time windows, corresponding roughly to N1m (140–220 ms), P2m (220–250 ms), an early P3 m window (250-340 ms), and a later P3m window (350–490 ms). These data were submitted to repeated-measures analysis of variance (ANOVA) with group (torture victims and survivors of organized violence with PTSD versus schizophrenia patients versus healthy participants) as a between subjects factor and affective category (pleasant, neutral, unpleasant) as within subjects factors, for the parameter RMS of each component. Time windows were selected on the basis of the grand mean RMS for those segments that contained the most pronounced magnetic field peaks.

HR data were evaluated with a repeated-measures ANOVA with affective category (pleasant, neutral, unpleasant) and phase (initial deceleration, following acceleration, final deceleration) as within subjects factors, and group (PTSD patients, schizophrenia patients, and healthy participants) as a between subjects factor.

Startle response magnitudes were also submitted to an ANOVA with group (PTSD patients, schizophrenia patients, healthy participants) as a between subjects factor and affective category (pleasant, neutral, unpleasant) and repetition (block 1 and block 2) as within subjects factors.

For the SAM pleasure and arousal ratings separate data analyses were performed using repeated measures analysis of variance (ANOVA) with affective category (within subjects), and group (between subjects factor).

Due to the problem of violation of homogeneity assumptions in repeated measures designs, the Greenhouse-Geisser (1959) (Geisser, 2003) epsilon correction was applied, where appropriate, and in these cases the ε-corrected P values are reported along with the original degrees of freedom. For all analyses, a difference was considered statistically significant when the P value was equal or less than 0.05.

In order to determine the nature of significant interaction effects, planned comparisons were preformed for simple main effects. Planned comparisons (contrast analyses) were used to examine the hypothesized differences in regard to affective valence and arousal. The script valence factor was parsed into orthogonal “quadratic” (i.e., pleasant/unpleasant versus neutral) contrasts – reflecting modulatory effects of arousal/activation and emotional valence, respectively (Bradley et al., 1990). Where no planned comparisons where conducted, the Tukey-Kramer method and the t-test were utilized to evaluate main effects and interactions.

Pearson correlation coefficients (r) were estimated and a linear regression was used to further explore the relation between MEG data and symptoms. Correlational analysis with clinical variables such as PTSD symptom level as measured with the PDS scale, the total intrusion scores, total avoidance scores, total scores of hyper-arousal, were performed in torture victims and survivors of organized violence with PTSD only, because of the low, restricted range of PTSD symptom severity in the healthy participants. The independent variables in these analyses consisted of clinical characteristics (total scores of PTSD, of intrusion, of hyper-arousal and of avoidance). In each analysis the dependent variable was an RMS difference values (computed separately for each time window) between: (a) the unpleasant and neutral conditions or (b) the pleasant and neutral pictures. Correlational analyses were also performed for HSCL-Anxiety, HSCL-Depression, and HSCL-Total scores for the PTSD patients using the same MEG parameters as described above. The significance levels were also set at corrected $p < 0.05$.

The relation between central nervous system activity and peripheral nervous system responses was further examined with correlation coefficients computed between the same RMS difference values and similarly computed HR response differences (pleasant minus neutral, unpleasant minus neutral).

The relation between HR and clinical ratings was assessed via correlations of HR response differences (pleasant minus neutral, unpleasant minus neutral) and the total scores of PDS- intrusion, of PDS-hyper-arousal, of PDS-avoidance, of HSCL-Anxiety, HSCL-Depression and HSCL-Total scores. Finally, Pearson correlations between the clinical ratings reflected in PDS-Scale, HSCL-Anxiety and HSCL-Total (for PTSD patients only) and startle response magnitude differences (pleasant minus neutral and unpleasant minus neutral data collapsed across blocks).

3.4 Results

3.4.1 Affective Ratings (SAM)

As expected SAM pleasure ratings differed as a function of affective category [$F(2,62) = 261.985$, $P < 0.0001$, □= 0.87], with pleasant pictures rated as most pleasant followed by neutral pictures, and unpleasant pictures rated as least pleasant [mean pleasure ratings: 7.12 ± 1.30 (pleasant), 5.0 ± 1.07 (neutral), 2.2 ± 0.78 (unpleasant), Tukey-Kramer $p < 0.05$ for all comparisons (Figure 3.3). For valence, there was no significant group difference.

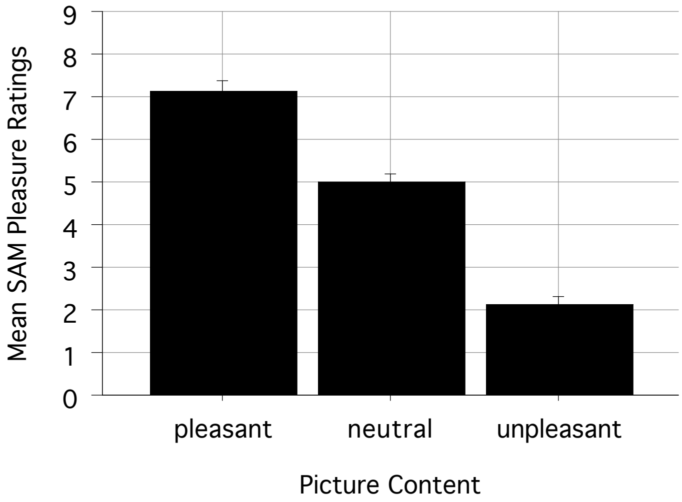

Figure 3.3. Mean SAM pleasure ratings (and standard errors) for each picture content (pleasant, neutral, unpleasant).

Arousal ratings also varied over affective categories [$F(2,62) = 70.2$, $P < 0.0001$, □= 0.87], with higher arousal ratings for unpleasant pictures rated as more arousing (6.95 ± 1.42 points) than neutral (4.29 ± 1.53 points) and pleasant pictures (4.05 ± 1.55 points) (Figure 3.4). Tukey-Kramer tests were significant ($p < 0.05$) for comparisons between unpleasant and pleasant, and for comparisons unpleasant and neutral pictures. The difference between pleasant and neutral pictures did not reach significance. Unpleasant pictures were rated as more arousing than pleasant pictures [$t(101) = 25.8$, $P < 0.001$], which was consistent with the IAPS normative ratings.

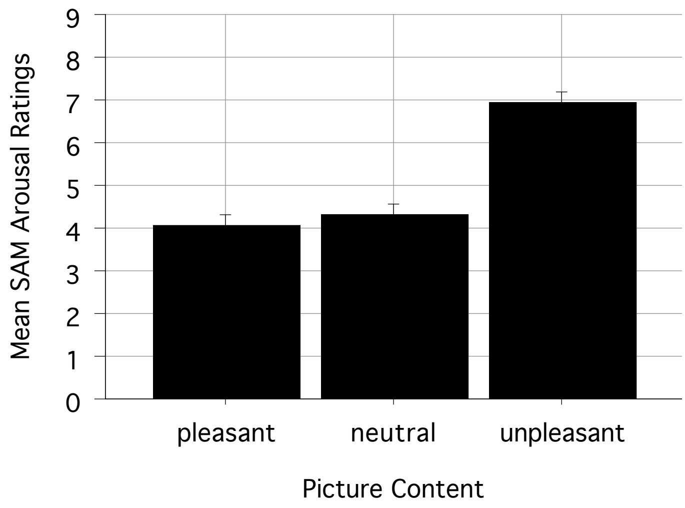

Figure 3.4: Mean SAM arousal ratings (and standard errors) for each picture content (pleasant, neutral, unpleasant).

Follow up simple main effects indicated a significant group effect for unpleasant pictures [$F(4,62) = 5.7$, $P < 0.001$, □= 0.76]. PTSD patients rated unpleasant pictures as more arousing (8.10 ± 0.38 points), compared to schizophrenia patients (6.10 ± 1.37 points) and control participants (6.57 ± 1.43 points).

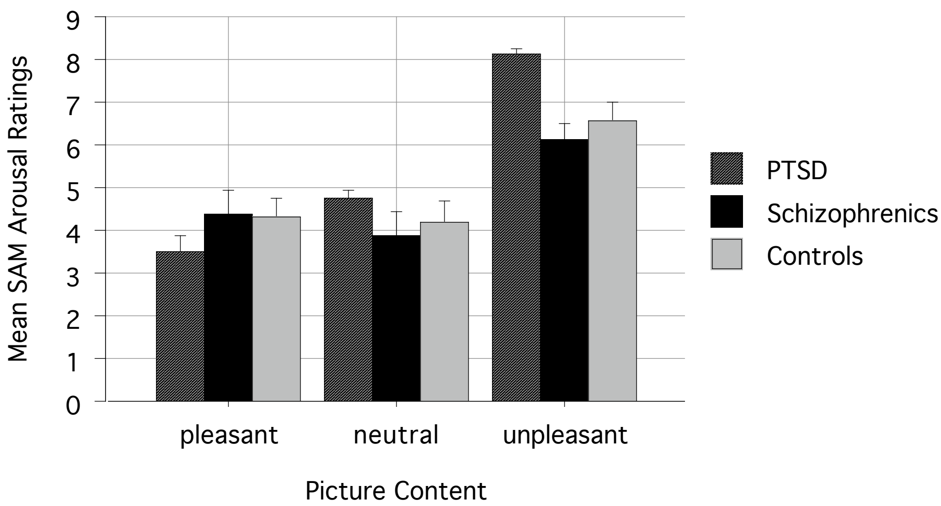

Figure 3.5: Mean SAM arousal ratings (and standard errors) for each picture content (pleasant, neutral, unpleasant) over groups.

3.4.2 Heart rate responses

As expected, the overall analysis of the cardiac waveforms resulted in a significant Affective Category by Group interaction [$F(4,70) = 8.8$, $P < 0.0001$, □ =0.57] elicited by unpleasant affective category in PTSD patients revealing an acceleratory response, which was absent in schizophrenia patients and control participants. The difference was characterized by an acceleration for the group in PTSD patients elicited by unpleasant pictures [mean bpm for each affective category in PTSD patients: (-1.2 ± 2.2) (pleasant), (-1.3 ± 1.8) (neutral), (.60 ± 1.8) (unpleasant), in schizophrenia patients: (-.91 ± .83) (pleasant), (-.71 ± 1.12) (neutral), (-1.08 ± .99) (unpleasant), and in control participants: (-1.1 ± 1.6) (pleasant), (-1.03 ± 1.64) (neutral), (-1.47 ± 1.53) (unpleasant), Tukey Kramer $p < 0.05$, for comparisons between unpleasant and pleasant, and unpleasant and neutral pictures]. There was no difference between neutral and pleasant pictures. The mean HR change over groups for each affective category is depicted in Figure 3.6.

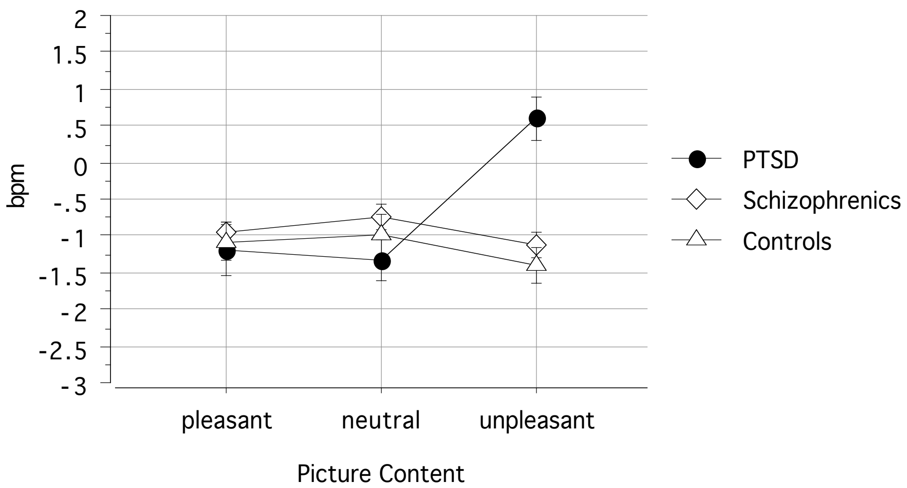

Figure 3.6: Mean heart rate change [bpm] for each picture content (pleasant, neutral, unpleasant) over groups.

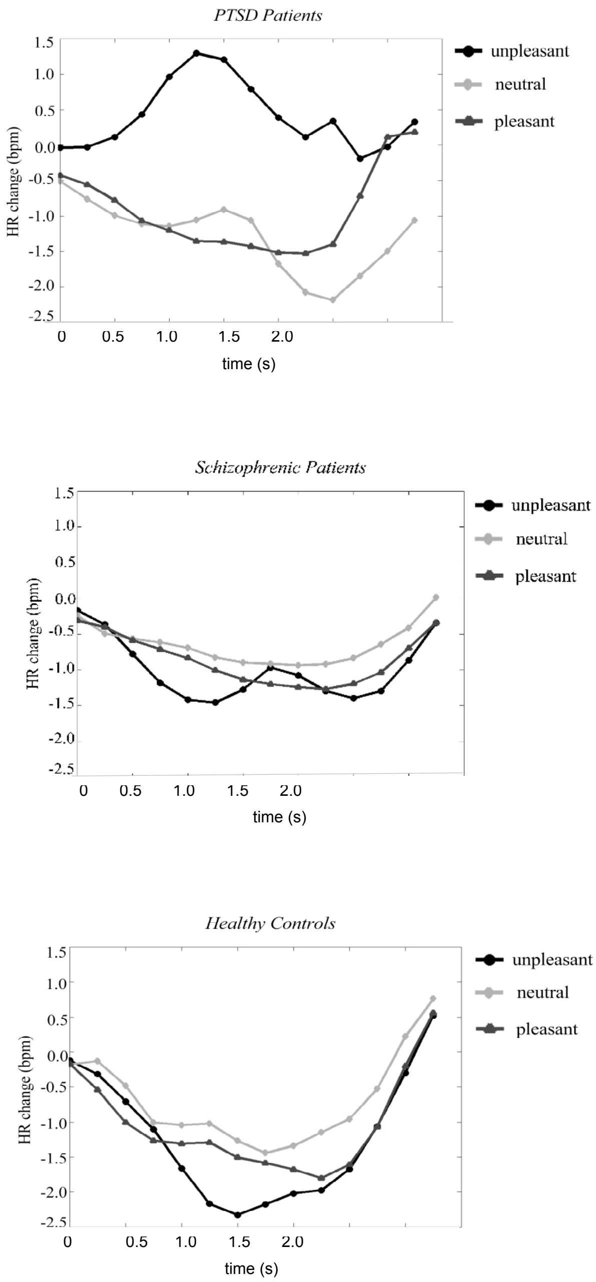

Figure: 3.7 Mean heart rate [bpm] change relative to pre-stimulus baseline across picture presentation time (2s) for each group and for each picture content (pleasant, neutral, unpleasant).

Furthermore, there was a three/- way interaction Affective Category by Phase and by Group [$F(8, 140) = 2.6$, $P < 0.01$, □= 0.49] with PTSD patients showing a stronger activation pattern in the three heart rate phases, the first, the following and the last 2s of heart rate changes during unpleasant affective category (Figure 3.8). This difference was characterized by a stronger initial deceleration, a subsequent relative acceleration, and a final deceleration: [mean initial deceleration PTSD patients: (-1.34 ± 2.3) (pleasant), (-1.28 ± 1.7) (neutral), (.43 ± 1.1) (unpleasant), in schizophrenia patients: (-.61 ± .46) (pleasant), (-.58 ± .89) (neutral), (-.89 ± 1.4) (unpleasant) and in control participants: (-1.1 ± 1.7) (pleasant), (-.79 ± 1.4) (neutral), (-.92 ± 1.4) (unpleasant)] and a test for single degree of freedom polynomials, which revealed a significant quadratic fit for mean initial deceleration in PTSD patients [$F(1,12) = 6.4$, $P < 0.002$]; [mean subsequent acceleration in PTSD patients: (-1.7 ± 2) (pleasant), (-.91 ± 1.7) (neutral), (1.1 ± 2.5) (unpleasant), in schizophrenia patients: (-1.1 ± .96) (pleasant), (-.89 ± 1.4) (neutral) (-1.2 ± .89) (unpleasant) and in control participants: (-1.4 ± 1.7) (pleasant), (-1.5 ± 1.9) (neutral), (-2.3 ± 1.6) (unpleasant)]; [mean final deceleration in PTSD patients (-.48 ± 2) (pleasant), (-1.8 ± 2) (neutral), (.24 ± 1.4) (unpleasant), in schizophrenia patients: (-1.00 ± .9) (pleasant), (-.67 ± 1.1) (neutral), (-1.2 ± .89) (unpleasant) and in control participants: (-.99 ± 1.5) (pleasant), (-.86 ± 1.7) (neutral), (-1.2 ± 1.4) (unpleasant)] and a test for single degree of freedom polynomials, which revealed a significant quadratic fit for final deceleration in PTSD patients [$F(1,12) = 7.7$, $P < 0.01$].

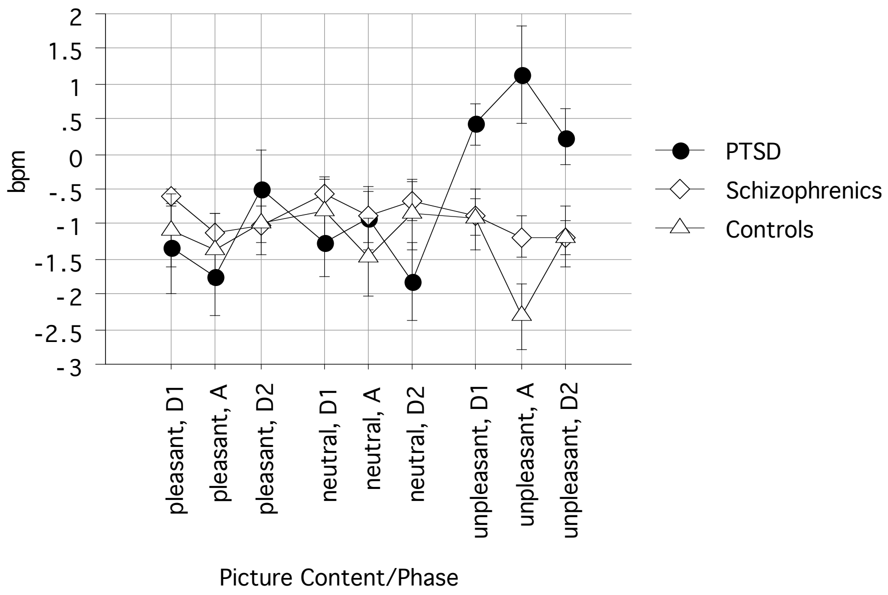

Figure 3.8: Mean heart rate change [bpm] for each picture content (pleasant, neutral, unpleasant) and phase over groups.

To decompose the Affective Category by Phase and by Group interaction, simple main effects were computed (Figure 3.9). Neither for pleasant affective category neither for neutral affective category were significant main effects observed. There was a main group effect in PTSD patients for unpleasant affective category [$F(2,35) = 9.9$, $p<0.0004$]. Differences were significant between PTSD and schizophrenia patients (Tukey-Kramer, $p>0.05$) and PTSD and control subjects (Tukey-Kramer, $p>0.05$); [mean bpm for unpleasant pictures: (.6 ± 1.8) (PTSD patients), (-1.1 ± 1) (schizophrenia patients), (-1.5 ± 1.5) (control participants)].

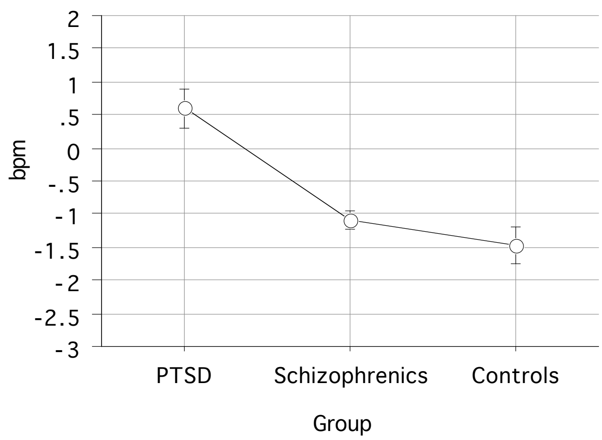

Figure 3.9: Mean heart rate change [bpm] over groups.

Furthermore, follow up simple main effects indicated a significant Phase by Group interaction for unpleasant pictures in PTSD patients [$F(4,70) = 5.1$, $p<0.001$] (Figure 3.10). PTSD patients showed a differential response pattern for unpleasant pictures; compared to schizophrenia patients and control participants; [mean initial deceleration for unpleasant pictures: (.4 ± 1.1) (PTSD patients), (-.92 ± .94) (schizophrenia patients), (-.92 ± 1.4) (control participants)], [mean following acceleration for unpleasant pictures: (1.1 ± 2.5) (PTSD patients), (-1.2 ± 1.2) (schizophrenia patients), (-2.3 ± 1.5) (control participants)], [mean final deceleration for unpleasant pictures: (.24 ± 1.4) (PTSD patients), (-1.2 ± .9) (schizophrenia patients), (-1.2 ± 1.4) (control participants)].

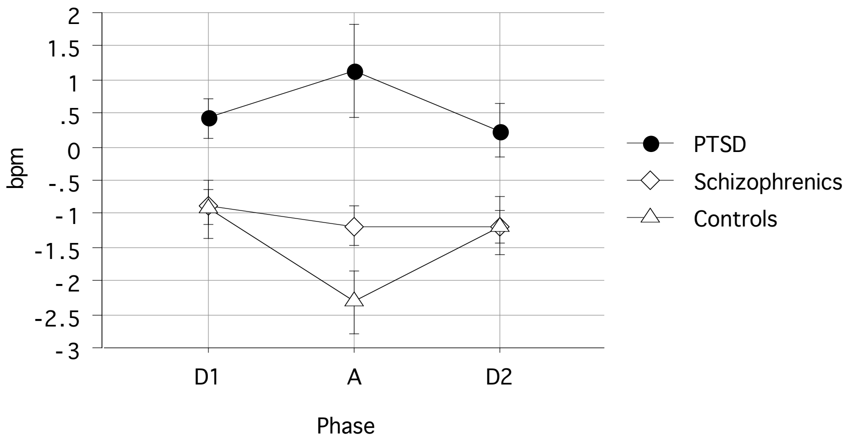

Figure 3.10: Mean heart change [bpm] for each phase over groups.

3.4.3 Startle response magnitudes: affective modulation

In startle responses during the first block of picture presentation (block 1) no effect of affective category was observed. However, a significant simple main effect of Group [$F(2,28) = 7.4$, $P < 0.002$, □ = 0.71] revealed that the blink magnitude was greater in PTSD patients during viewing for each picture content (pleasant, neutral and unpleasant), and that blinks were larger during unpleasant and pleasant picture category, followed by neutral picture category, and a test for single degree of freedom polynomials revealed a significant quadratic fit block 1 in PTSD patients [F(1,14) = 8.2, P < 0.002], [mean startle responses in PTSD patients: (1.8 ± .77) (pleasant), (1.6 ± .64) (neutral), (2.12 ± .81), mean startle responses in schizophrenia patients (1.2 ± 1.7 (pleasant), (.80 ± .56) (neutral), (.86 ± 51) (unpleasant) and in control participants (1.80 ± .71) (pleasant), (1.34 ± .57), (neutral), (1.47 ± .45) (unpleasant), Tukey-Kramer P < 0.05 for comparisons PTSD patients and schizophrenia patients]. There was no significant difference between the other groups. Moreover, there was no significant difference among affective categories (Figure 3.11).

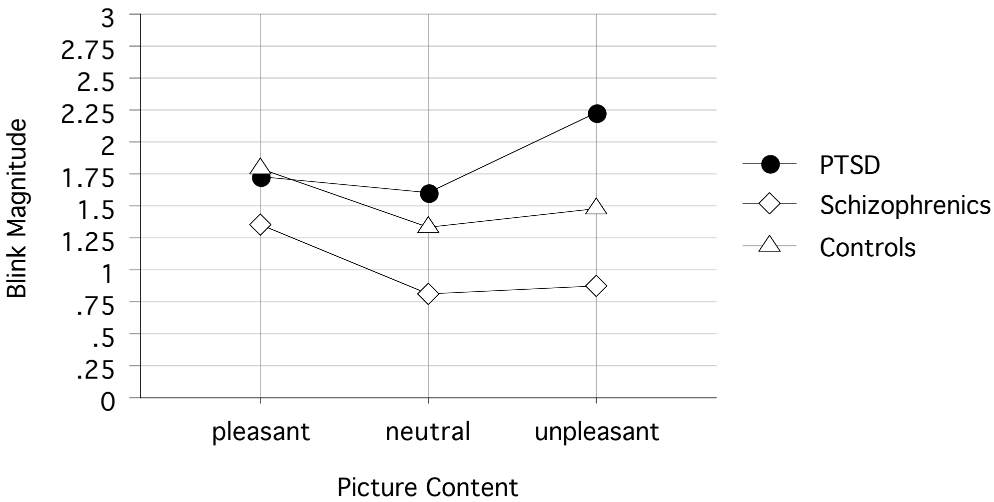

Figure 3.11: Mean blink magnitude over groups for each picture content (pleasant, neutral, unpleasant) in first block.

A significant main effect of diagnosis was also observed in block 2 during picture presentation [F(2,28) = 8.8, P < 0.001, □=0.98]. PTSD patients showed augmented startle responses when compared to schizophrenia patients [t(64) = 5.4, P < 0.001], and to control participants [t(55) = -3.1, P < 0.003]. Control participants differed also from schizophrenia patients displaying stronger startle responses [t(61) = 3.77, P < 0.004]. Furthermore, there was a significant interaction between Affective Category and Group [F(4,56) = 2.40, P < 0.006, □ =0.98] and a quadratic trend [F(2,28) = 6.4, P < 0.003] reflecting stronger startle responses for each affective category in PTSD patients, compared to schizophrenia patients and to control participants [mean startle responses in PTSD patients: (2.02±1.62) (pleasant), (1.59± 1.07) (neutral), (2.33±1.41) (unpleasant), in schizophrenia patients: (.47±.40) (pleasant), (.76±.87) (neutral), (.57±.38) (unpleasant), and in control participants: (1.23±.64) (pleasant), (1.14±.38) (neutral), (.99±.32) (unpleasant), Tukey-Kramer $p < 0.05$ for comparisons between PTSD patients and schizophrenia patients]. There was no difference between PTSD patients and control participants, schizophrenia patients and control participants. There was also no difference among affective categories. The trend analyses indicated that the valence modulation is driven primarily by the high activation in response to unpleasant pictures with apparent differences between unpleasant and neutral pictures (Figure 3.12).

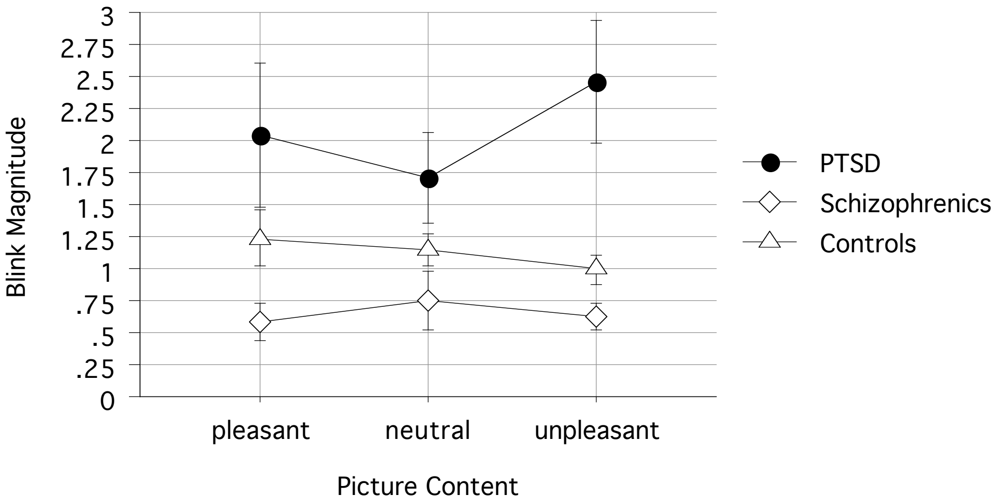

Figure 3.12: Mean blink magnitude over groups for each picture content (pleasant,neutral, unpleasant) in second block.

Pearson correlations between HSCL-Anxiety ratings and startle response magnitude over the two blocks of picture presentation revealed a significant positive correlation between HSCL-Anxiety ratings and the magnitude for the startle response for the difference unpleasant minus neutral [$r = .62$, $df = 1$, $p<0.05$]. As indicated in the description of variables in the analyses section there were no significant correlations between startle magnitude and HSCL-Total scores or PDS symptom scores.

3.4.4 Correlations between clinical ratings and heart rate responses

Clinical ratings were significantly correlated with HR responses. As indicated in the description of variables in the analyses section avoidance symptoms were positively correlated with mean HR responses for the difference unpleasant minus neutral [$r=.66$, $df=1$, $P < 0.003$]. There were no significant correlations between other clinical ratings and HR responses (Figure 3.13).

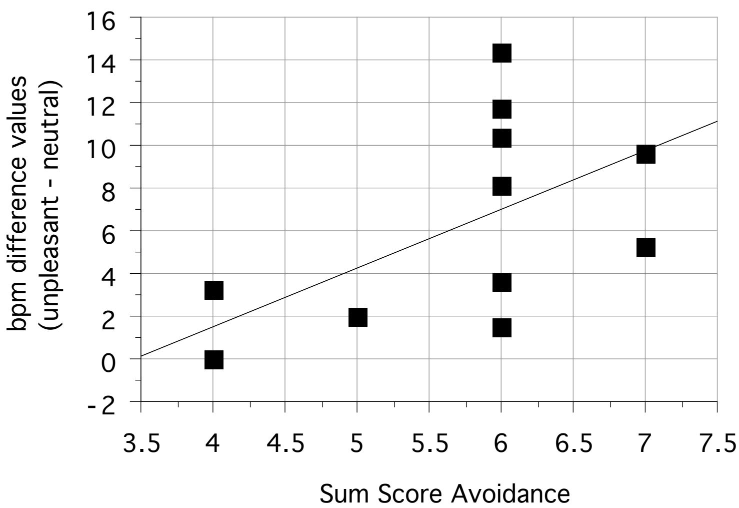

Figure 3.13: Heart rate change [bpm] difference values (unpleasant – neutral) correlations with sum score avoidance as measured by PDS.

3.4.5 MEG data

Root mean square values of magnetic flux recorded by each set of magnetic sensors are shown in Figures 3.14, 3.15, 3.16. Given our hypothesis for differential magnetocortical activity in processing different emotional contents, the focus of the present study was on effects of stimulus type on RMS values recorded by pre-selected sets of sensors at each time window after stimulus onset.

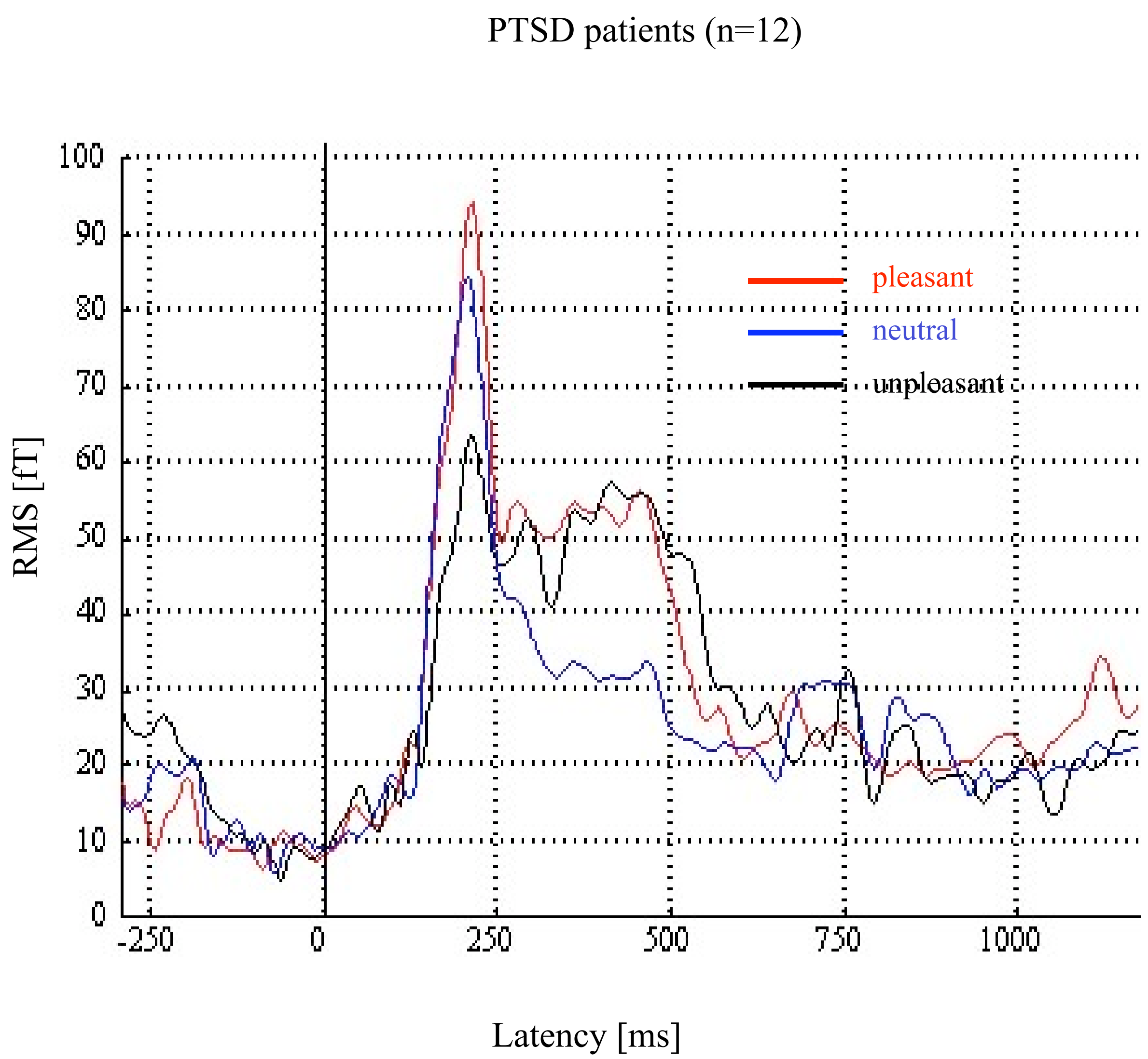

Figure 3.14: Grand Mean (n=12) RMS [fT] (see Equation 3.1) of the magnetic field strength obtained for torture victims and survivors of organized violence with PTSD for each picture content (pleasant, neutral, unpleasant).

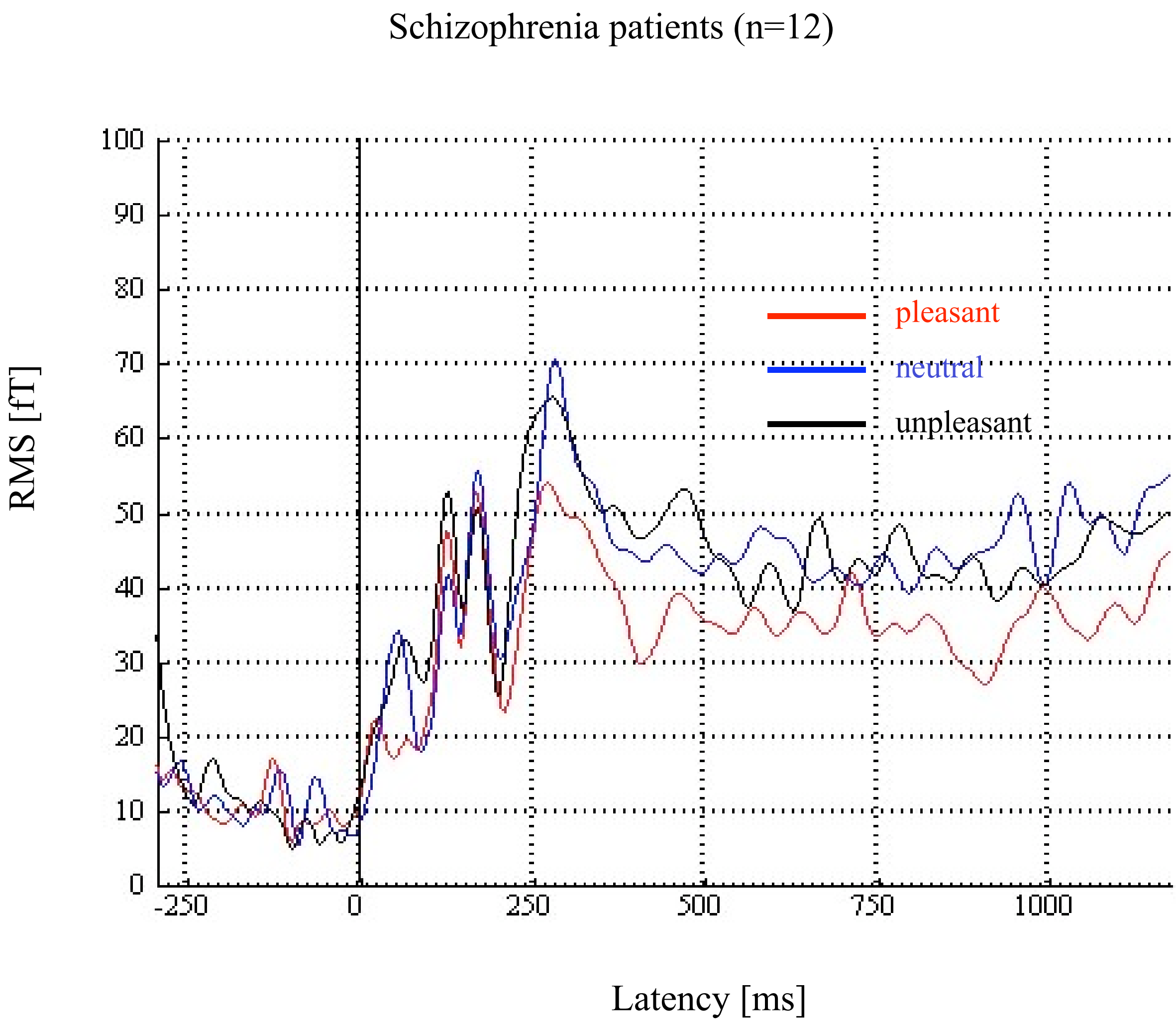

Figure 3.15: Grand Mean (n=12) RMS [fT] (see Equation 3.1) of the magnetic field strength obtained for schizophrenia patients for each picture content (pleasant, neutral, unpleasant).

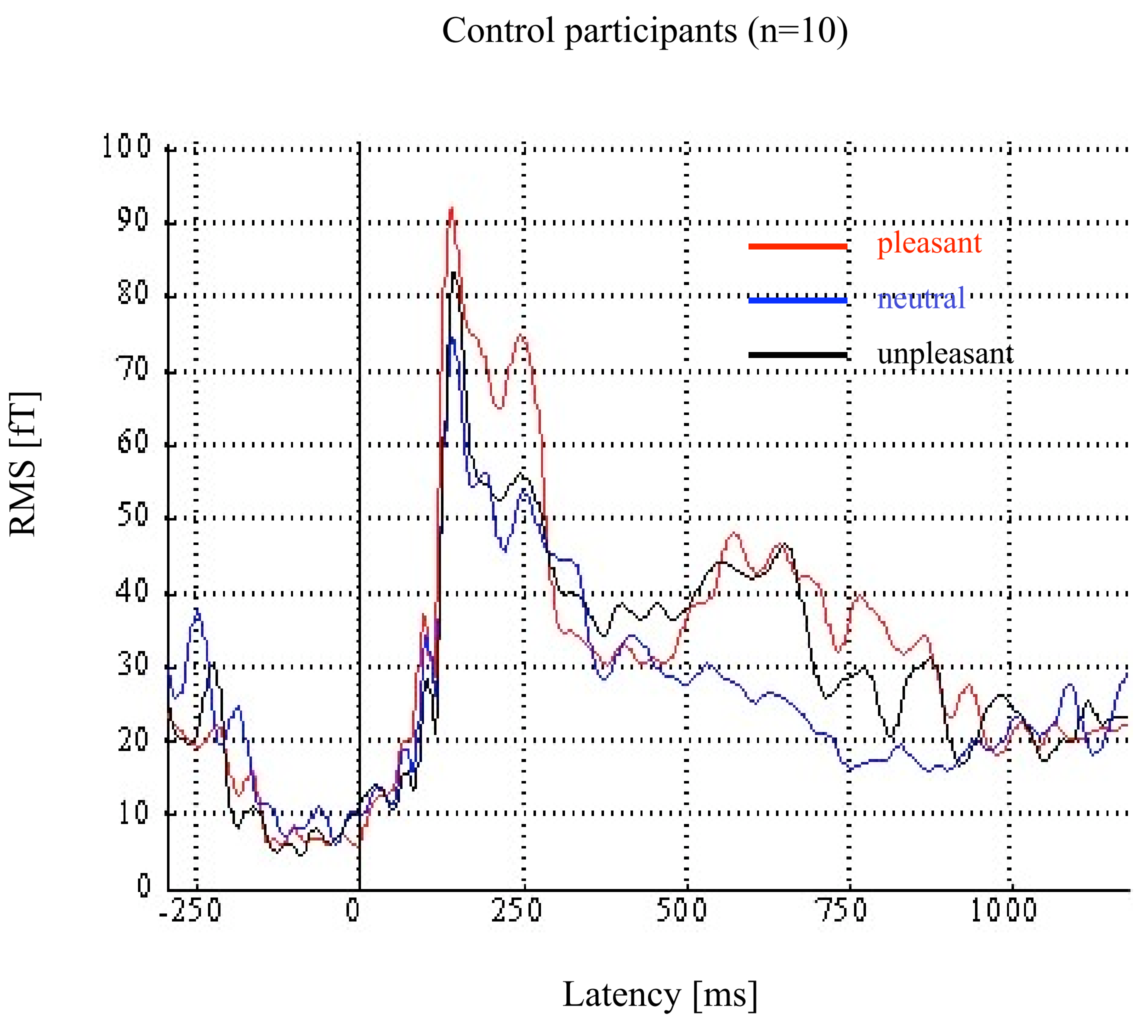

Figure 3.16: Grand Mean (n=10) RMS [fT] (see Equation 3.1) of the magnetic field strength obtained for healthy participants for each picture content (pleasant, neutral, unpleasant).

N1m Time Window

During the N1m time window (140-220 ms) the main effect of stimulus category approached statistical significance [$F(2,62) = 2.8$, $p<0.06$, □= 0.90]. This trend was evident regardless of group and was characterized by an enhancement of the N1 amplitude by pleasant pictures (149.2±61.5 fT) as compared to unpleasant pictures (132.8±48.3 fT; Tukey-Kramer, $P<0.05$). There was no difference between neutral and pleasant pictures, or between neutral and unpleasant pictures (Figure 3.17).

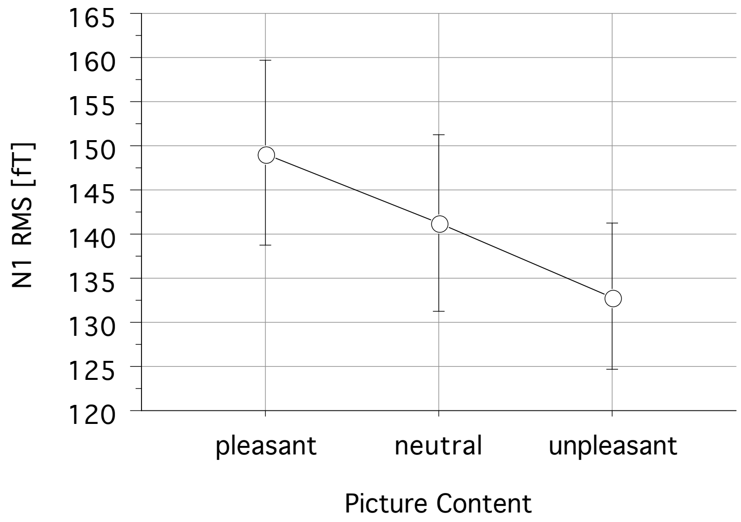

Figure 3.17: Mean N1m RMS values [fT] for each picture content (pleasant, neutral, unpleasant).

P2m Time window

While there were no significant main effects or interactions during the P2m window, planned one-way repeated measures ANOVAs for Affective Category within each Group revealed a significant quadratic trend for PTSD patients [$F(1,11) = 6.5$, $p<0.02$] (Figure 3.18). As a group these patients showed higher RMS when viewing of both pleasant (114.3±55.3 fT) and unpleasant pictures (120.1±70.5 fT) as compared to neutral pictures (96.7±41.8 fT).

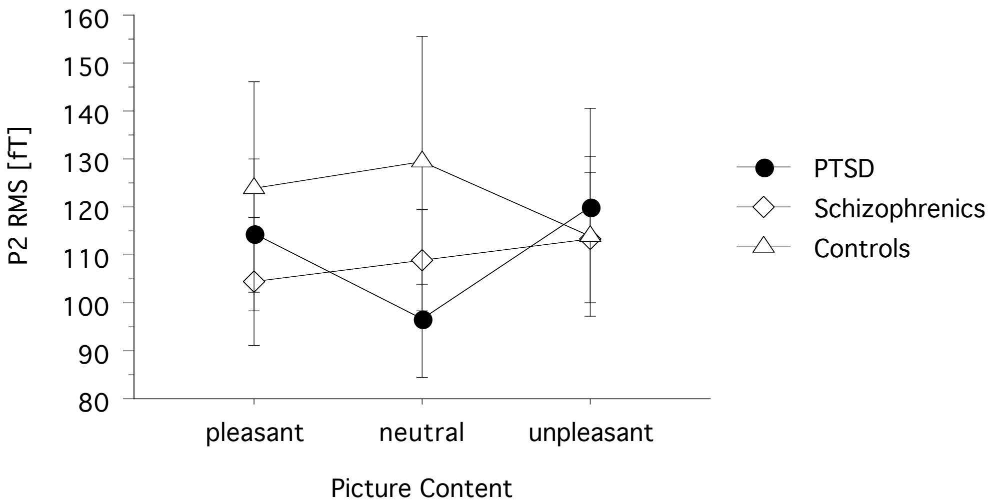

Figure 3.18: Mean P2m RMS values [fT] for each picture content (pleasant, neutral, unpleasant).

Early P3m Time Window

Pronounced main effects of Affective Category were also seen in the early P3 window (250–340 ms) [$F(2,62) = 5.2$, $P < 0.001$, □= 0.82] reflecting greater RMS for emotive pictures (either pleasant: 73.1 ± 41.6 fT or unpleasant: 70.7 ± 42.8 fT) as compared to neutral pictures, (59.9 ± 34.42 fT, Tukey-Kramer $P < 0.05$ for both comparisons) (Figure 3.19).

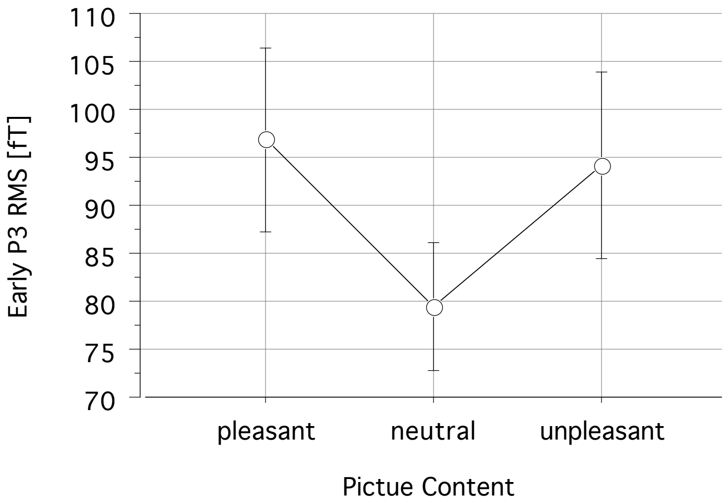

Figure 3.19: Mean early P3m RMS [fT] values for each picture content (pleasant, neutral, unpleasant).

Late P3m Time Window

Finally, the late P3m deflection starting at 350 ms post-stimulus onset exhibited an Affective Category by Group interaction [$F(4,62) = 3.5$, $P < 0.01$, □=0.99] (Figure 3.20). This difference revealed that PTSD patients exhibited an affect modulation with higher amplitudes as related to viewing of both pleasant and unpleasant pictures [mean late P3 amplitudes in PTSD subjects: 64.19±30.4 (pleasant), 47.01±26.2 (neutral), 61.05±41.04 (unpleasant); mean late P3 amplitudes in subjects with schizophrenia 54.65±27.5 (pleasant), 58.2±28.6 (neutral), 53.7±29.4 (unpleasant); mean late P3 amplitudes in control subjects 71.6±31.7 (pleasant), 55.0±35.1 (neutral), 38.8±18.9 (unpleasant), Tukey-Kramer $p<0.05$ for comparisons between pleasant and unpleasant pictures]. Differences related to picture content were elicited by pleasant and unpleasant pictures. There was no difference between groups.

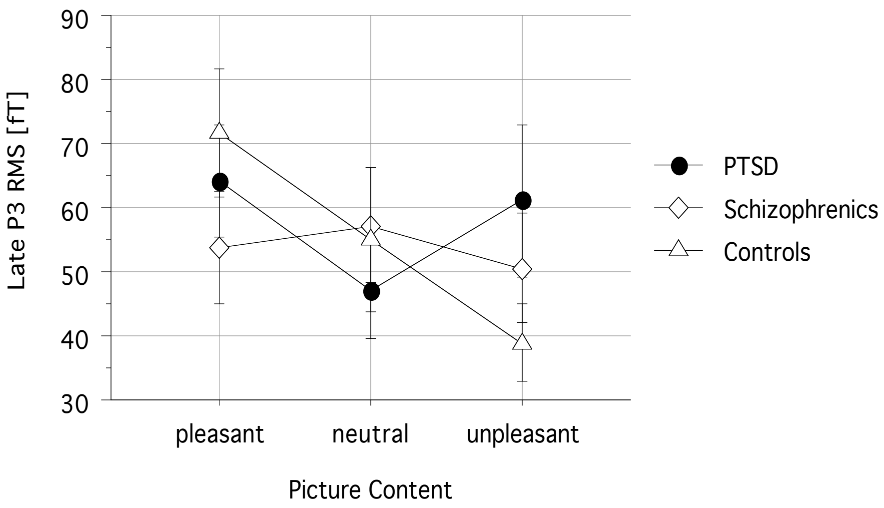

Figure 3.20: Mean late P3m RMS [fT] values for each picture content content (pleasant, neutral, unpleasant) over groups.

3.4.6 Correlations between clinical measures in PTSD patients

Within the PTSD group there were significant correlations between PDS-Intrusion and HSCL-anxiety [r= .72, df =1, P < 0.006], between PDS-Avoidance and HSCL-depression [r= .63, df = 1, p < 0.03], and between PDS-arousal and HSCL-anxiety [r= .67, df = 1, P < 0.01].

3.4.7 Correlations between MEG data and clinical ratings in PTSD patients

Among PTSD patients, there was a significant negative correlation between the total score of avoidance of PDS scale and the RMS difference value (unpleasant – neutral) for the N1m component [r = -.637, df=1, P < 0.02]. This result indicates that the amplified viewing of neutral pictures showed a significant inverse relationship with the total score of avoidance of PDS and therefore the amplified N1m for neutral pictures was predictive of high avoidance scores in torture victims and survivors of organized violence with PTSD (Figure 3.21).

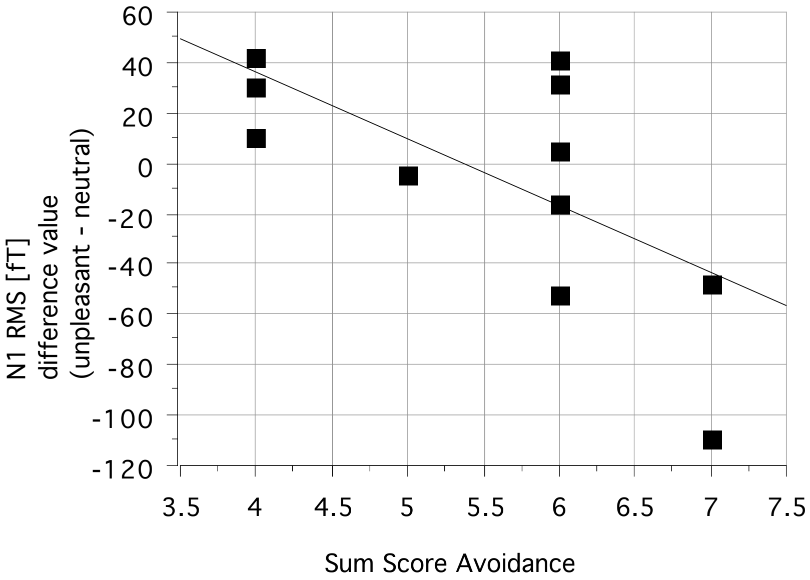

Figure 3.21: N1m RMS [fT] difference values (unpleasant – neutral) correlations with sum score avoidance symptoms measured by PDS.

This correlation was supported further by the clinical data, which showed that PDS-Avoidance was highly correlated with HSCL-depression [r= .63, df =1, P < 0.03].

There was also a significant negative correlation between the total depression score of the HSCL-25 and the RMS value for the N1m component for the difference unpleasant to neutral pictures [r = -.693, df = 1, P < 0.01], indicating that the amplified viewing of neutral pictures was significantly associated to more severe depression symptoms in PTSD patients (Figure 3.22). Furthermore, there was a significant negative correlation between the total score of HSCL-25 and the RMS values of the N1m component for the difference unpleasant to neutral pictures [r = -.628, df = 1, P <0.03]. This result indicates that the amplified N1m component for neutral pictures showed a significant inverse relationship with total HSCL-25 score.

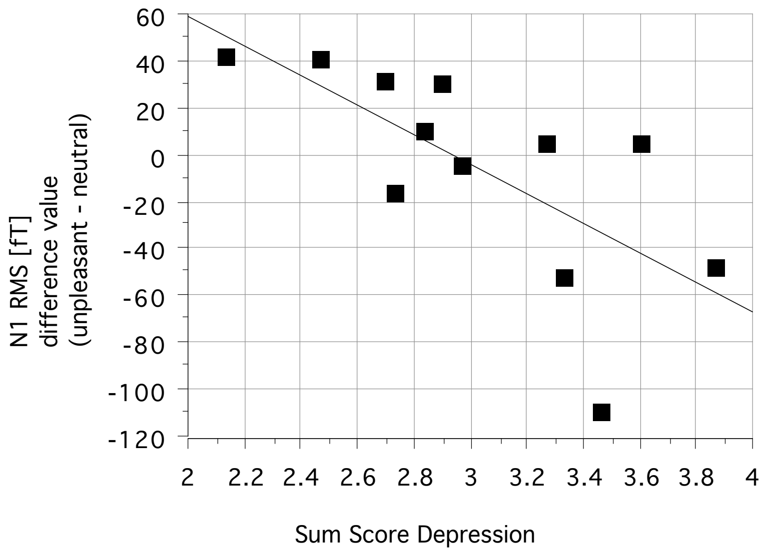

Figure 3.22: N1m RMS [fT] difference values (unpleasant – neutral) correlations with sum score depression measured by HSCL.

Furthermore, there was also a significant positive correlation between the total anxiety score of the HSCL-25 and the P2m component for the difference pleasant to neutral [$r = .582$, $df = 1$, $P < 0.04$]. This indicates that the amplified values for pleasant pictures were significantly correlated with higher anxiety symptoms in torture victims and survivors of organized violence with PTSD (Figure 3.23).

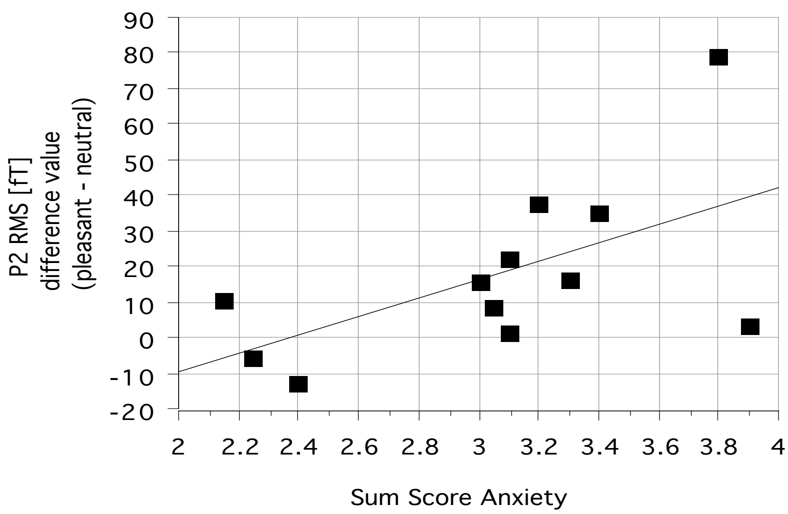

Figure 3.23: P2m RMS [fT] difference value (pleasant – neutral) correlations with sum score anxiety measured by HSCL.

3.4.8 MEG correlations with heart rate responses

Simple linear regression between MEG responses during picture viewing and HR responses revealed a significant negative correlation between the brain responses in the late P3m component and the HR responses for this latency ($r = -.590$, $df = 1$, $P < 0.04$) (Figure 3.24). The dependent variable, the late P3m component, for the difference pleasant minus neutral, was negatively correlated with HR responses for the difference pleasant minus neutral pictures. This result indicates that the decrease of the difference in the brain responses between pleasant minus neutral pictures viewing showed a significant negative correlation with the same difference within the HR response. Amplified viewing of pleasant pictures was correlated with deceleration while viewing of neutral pictures was correlated with acceleration. The other components, N1m, P2m, early P3m, were not significantly correlated with the HR responses.

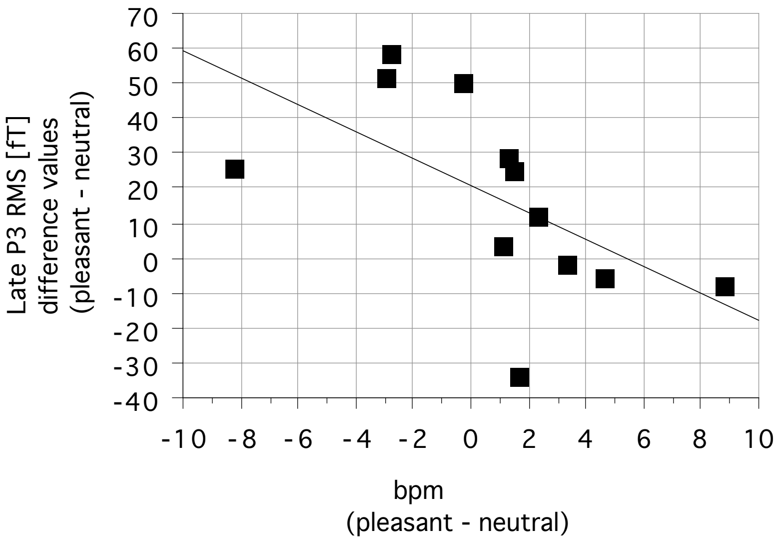

Figure 3.24: RMS [fT] difference values (pleasant – neutral) correlations with bpm difference values (pleasant – neutral).

3.5 Discussion

The overall aim of this study was to investigate information-processing differences during affective picture presentation, using MEG in torture victims and survivors of organized violence with PTSD. In the present study, we addressed the question of whether the processing of emotional stimuli represents in PTSD an abnormal pattern of central nervous processing or whether reflect a general abnormality linked to trauma-related stimuli.

This study involved twelve torture victims and survivors of organized violence with PTSD, twelve schizophrenia subjects as a clinical control group, and a matched control cohort allowing us to not only detect differential responses to emotional stimuli on a single subject group, but also to investigate differences in the activation networks of torture victims and survivors of organized violence relative to schizophrenia patients and healthy participants. Examining the differences between affective contents in terms of magnetocortical activity in four time windows, we found a changing preponderance over the course of time regarding affective contents between groups. Findings obtained with RMS values for time windows of interest converged regarding these effects.

In the earliest time window (N1) there was displayed more reactivity to emotionally (pleasant) arousing pictures then has been reported earlier for comparable time ranges in an EEG study (Keil et al., 2002). Likewise, in a visual hemifield design employing IAPS pictures Keil et al. (2001) (Keil et al., 2001) found an N1 enhancement for arousing, compared to neutral pictures. Moreover, early event-related potentials (ERP) differences between arousing and neutral stimuli have been reported by Junghöfer et al. who presented IAPS pictures in a rapid visual stream (Junghofer et al., 2001).

Moreover, the response pattern for N1m component revealed no significant differences among groups. Interestingly enough, in PTSD subjects the N1m component revealed higher activation patterns for pleasant and neutral pictures followed by unpleasant pictures. It could be claimed that this finding implies disturbances in pre-attentive processes in PTSD subjects (Felmingham, Bryant, Kendall, & Gordon, 2002; Lewine et al., 1997). For instance, PTSD subjects revealed reduced sensory gating (Neylan et al., 1999) and increased mismatch negativity (Morgan & Grillon, 1999) to neutral auditory stimuli. In our study this finding could be attributed to the significantly negative correlation we found between the N1 component and the total avoidance score. Although previous studies, such as Attias et al. (Attias, Bleich, Furman et al., 1996) have studied the brain visual hypersensitivity as reflected in the early N1 potential, they found that in PTSD subjects combat-related pictures evoked the largest N1 amplitudes at all electrode sites. This argues against our data, although these data do not counter the idea that N1 visual component results in smaller cortical responses in PTSD subjects; rather, they suggest that amplified N1m responses for viewing neutral pictures are a predictor of high total avoidance scores. Similarly, in another study, ERP's were examined to angry and neutral facial expressions in controls and in PTSD subjects (Felmingham, Bryant, & Gordon, 2003). The control group revealed increased activity at early N1 component to angry facial expression whereas the PTSD group failed to differentiate between neutral and angry expressions. Further on, when compared to controls, the PTSD group showed reduced responses to angry faces for the early N1 component. The authors attributed these findings to the difficulty that PTSD subjects shown discriminating generalized threat and non-threatening stimuli.

The P2m (220-250 ms) component showed an interaction between Affective Category and by Group, displaying more reactivity relative to emotionally arousing pictures for PTSD subjects. It seems likely that the P2m component was sensitive to the valence component of affective response particularly in PTSD subjects; emotional slides both pleasant and unpleasant yielded a larger positivity as compared to neutral ones. Likewise, increased P2 amplitudes in response to high arousing pictures have been reported in a visual ERP work by Jünghöfer et al. (Junghofer et al., 2001). In another study, Palomba et al. (Palomba et al., 1997) did not find any valence effect for the visual P2 peak amplitudes whereas the earliest emotional effect in their study was found about 282ms after stimulus onset. However, there is little literature addressing the visual P2 component in PTSD subjects. To our knowledge, Attias et al. (Attias, Bleich, Furman et al., 1996) studied P2 components in the form of a modified oddball paradigm with pictorial stimuli, between PTSD patients and controls, yet without differences between groups. Most of what is known about the P2 component is based on studies that have investigated the auditory P2 in PTSD subjects. In an auditory paradigm, Paige et al. (1990) (Paige et al., 1990) found that Vietnam veterans with or without PTSD had different evoked potentials (EPs) to increasing intensity of an auditory tone. Veterans with PTSD exhibited decreased P2 amplitude with increasing sound volume, whereas veterans without PTSD showed increased P2 amplitude with increased sound volume. This diminution in the P2 amplitude is positively associated with levels of anxiety, but not depression or measures of PTSD symptoms. Paige et al. (1990) argue that the diminution of P2 amplitude in response to intense auditory stimuli reflects a sensitivity to intense stimuli that activates a process of protective inhibition; the nervous system inhibits stimulation that would otherwise overload its capacity for accurate discrimination and pose troublesome dealing with further information (Paige et al., 1990).

Pronounced main effects of picture content were also seen in the early P3m time window (250-340 ms) as well as in the later P3m time window (350-490 ms) without differences between groups. As found in previous studies, differences in the magnitude of positive going potential in time windows later than 300 ms were found as a function of emotional arousal (Cuthbert et al., 2000; Keil et al., 2002). Moreover, PTSD subjects displayed more reactivity to emotionally arousing (pleasant or unpleasant) pictures over the late time windows, which are thought to reflect cognitive processing. Consistent to our hypothesis and previous research, current findings suggest that cortical responses in PTSD subjects were specifically sensitive to the valence component of affective response over P3m time windows.

Emerging data from several studies are showing that PTSD is associated with increased neurophysiological activity in response to emotional or trauma-relevant stimuli (Attias, Bleich, & Gilat, 1996; Bleich et al., 1996; Blomhoff et al., 1998; Bremner, Staib et al., 1999). Using a modified oddball task with pictorial stimuli Attias and his colleagues (1996) found that a combat probe, but not neutral non-target stimuli elicited increased P3 amplitude at midline sites among PTSD-diagnosed combat veterans as compared to veterans without mental disorders. The authors suggested that these findings supported the hypothesis that PTSD subjects perform a specific information-processing pattern towards to traumatic stimuli (Attias, Bleich, & Gilat, 1996). Altogether, this studies support the contribution of processing to the increased sensitivity to trauma-related information in PTSD (Hendler et al., 2003).

Startle Reponses

The eye-blink data replicated the results of many other studies on affective modulation of human startle. The present study found blink attenuation to acoustic probes presented during pleasant picture viewing and blink potentiation to acoustic probes presented during unpleasant picture viewing (Balaban & Taussig, 1994; Bradley & Lang, 2000). The data of this study add to the growing body of evidence supporting the existence of an exaggerated startle response in PTSD patients. The positive correlation we found between startle response for the difference unpleasant minus neutral and the total HSCL-Anxiety score suggests that startle and anxiety are core clinical features of the human psychological response to traumatic experiences (Morgan, Grillon, Lubin, & Southwick, 1997). Moreover, it seems that exaggerated startle potentiation in PTSD patients resulted from unpleasant and highly arousing pictures (Bradley et al., 1990). We may speculate that the exaggerated startle response seen in PTSD patients is part of a conditioned response to stressful situations or stimuli reminiscent of trauma (Hitchcock, Sananes, & Davis, 1989). It is conceivable that PTSD patients suffer from a dysregulation of hippocampal activity that leads to an abnormal processing of contextual information (Morgan, Grillon, Southwick, Davis, & Charney, 1995). Such a hypothesis could account for the increased anxiety response and for the increased startle response displayed by PTSD patients in the more aversive experimental environment of the MEG chamber. It is also possible that the novelty of the environment was responsible for the exaggerated startle responses seen in PTSD patients. Lang and colleagues have recently reported that a general startle sensitivity may characterize individuals with negative affect. They further speculated that these individuals might be especially vigilant and apprehensive in novel situations (P. J. Lang et al., 2000). The exaggerated startle response seen PTSD patients might be due to a combination of an abnormal processing of contextual information and of a novel environment. The pattern of results suggested that, overall PTSD patients exhibited an inhibition of blink magnitude during pleasant pictures, as compared to neutral pictures, whereas unpleasant pictures elicited an increased facilitation of the blink magnitude. It should be emphasized that in the present study, in the first block of picture presentation, although the startle reflex in PTSD patients was significantly greater than in schizophrenia patients and control subjects, we did not find any significant affective valence with group interaction. On the other hand, in the second block of picture presentation the overall eye-blink magnitude was significantly greater in PTSD patients than in schizophrenia patients and a significant interaction was observed between affective category and group. Moreover, unlike PTSD patients who exhibited larger startle responses while viewing unpleasant than while neutral pictures, schizophrenia patients showed an abnormal pattern of blink reflex modulation.

Accordingly, schizophrenia patients did not exhibit any difference in their blink amplitudes to unpleasant and neutral pictures. On the other hand, in the first block of picture presentation, blink amplitudes were smaller while viewing pleasant pictures than while viewing unpleasant pictures, whereas they did not differ from blinks related to viewing neutral pictures.

Heart Rate Responses

Analysis of cardiac responses yielded several important results. As in previous studies, a classic triphasic waveform (Gatchel & Lang, 1973) was obtained, consisting of an initial deceleration, subsequent acceleration, and a secondary deceleration time. Average HR did significantly vary among groups. Aversive pictures usually generate a sustained heart rate deceleration over the whole picture presentation time with al less clear triphasic pattern as compared to neutral and pleasant pictures. Pleasant pictures usually provoke a greater initial deceleration and a more pronounced accelerative component than neutral pictures (Bradley, Codispoti, Cuthbert, & Lang, 2001). In our study heart rate response as function of picture valence differed dramatically in PTSD subjects. The groups differed significantly from one other with regard to affective picture content. PTSD subjects showed greater HR acceleration to high-arousing unpleasant pictures as compared to schizophrenia and to control subjects. The elevated HR responses to unpleasant pictorial stimuli are consistent with other studies that showed that HR increased in trauma victims in response to pictorial representations (Buckley & Kaloupek, 2001). Blanchard et al. (E. B. Blanchard et al., 1991) also observed apparent basal elevations in cardiovascular activity, particularly HR, shown by PTSD groups as compared to control groups during the resting baseline periods.

Furthermore, in line with other studies heart rate changes in schizophrenic subjects and in controls did not differ significantly (Schlenker, Cohen, & Hopmann, 1995; Volz, Hamm, Kirsch, & Rey, 2003) with regard to affective valence. Moreover, the visceral responsivity of schizophrenic patients is generally reduced relative to healthy control subjects. Despite the similarities between schizophrenic patients and controls, schizophrenic patients show an abnormal pattern of HR reactions during the exposure to pleasant, neutral and unpleasant pictures. Unlike control subjects, who showed a prolonged deceleration component relative to unpleasant pictures, followed by neutral and unpleasant pictures, schizophrenic patients exhibited a diminished pattern of affective reactivity. This attenuation of visceral responsivity in schizophrenia patients may account for the decreased modulation caused by stimulus contents.

Cortical responses correlate with HR responses during picture viewing

Examining MEG correlates of affective picture viewing with HR responses revealed a significant negative correlation in the late P3 time window with HR responses. The present findings show that patterns of both increased and decreased activation in cortical brain systems are functionally related to ongoing changes in cardiac autonomic activity (Gianaros et al., 2004). This suggestion is supported by the finding that late P3m responses for the difference pleasant minus neutral correlated with increased heart rate responses. Those PTSD subjects who showed higher cortical positivity to neutral pictures also presented higher heart rate acceleration. For the early components we did not find any significant correlations between MEG and HR responses. It is also reasonable that late P3m component was associated with HR changes to a greater extent than early components, due to different response latencies of the two systems (Palomba et al., 1997). Furthermore, in the context of the difference pleasant minus neutral the increased HR activity for neutral pictures in this time window may reflect a pattern of a failure to habituate to non-threat stimuli (hypervigilance) and defensive reactions (HR acceleration) to the presentation of neutral stimuli. We may further speculate that the enhanced responses to neutral pictures may be associated with sustained anxious apprehension. This result is also consistent with the significant positive correlation we found between the total PDS-avoidance score and the HR responses for the difference unpleasant minus neutral. Taken together, accelerating HR responses to neutral pictures for the late P3 time window and the correlation between PDS- avoidance score and accelerating cardiac autonomic activity in PTSD patients suggest that the relationships between cortical activity and cardiac autonomic activity and between clinical measures and cardiac autonomic activity act as a network to support a broad range of cognitive and emotional processes. Furthermore, early studies have often reported in various studies that patients with anxiety disorders showed exaggerated or prolonged responses to typical laboratory stressors (Berntson et al., 1998). To evidence patients with anxiety disorders have exhibited a slower rate of habituation of autonomic responses over trials (Rasmussen & Jacobs, 1986). Further evidence of the potential specificity of anxiety disorders comes from the demonstration that PTSD patients display a pattern of autonomic response roughly paralleling their pattern of behavioral/ affective reactivity (Hoehn-Saric & McLeod, 1988; Hoehn-Saric, McLeod, & Zimmerli, 1989). Moreover, studies have demonstrated that PTSD patients may show a more generalized avoidance or withdrawal tendencies, and have been reported to display exaggerated cardioacceleratory responses to non-signal auditory stimuli (Morgan et al., 1995; Paige et al., 1990; Shalev, Orr, & Pitman, 1992).

To summarize, the current results underscore that cortical responses during picture viewing correlate with changes in cardiac autonomic activity in PTSD patients. To our knowledge, this study employed magnetoencephalogrpahy and evoked changes in cortical activity and corresponding changes in heart rate responses in PTSD patients.

Magnetocortical responses during picture viewing in torture victims and survivors of organized violence with PTSD correlate with clinical data

The unique aspect of the present study is the fact that the magneto-cortical responses in the N1m time window in PTSD subjects revealed a significant negative correlation with the total avoidance score. The discrepancy of findings, regarding enhanced fear potentiation at a very early stage of visual processing (P. J. Lang, Bradley et al., 1998b) could be related to disturbances in pre-attentive processes in PTSD (Felmingham et al., 2002). These particular findings however are compatible with the notion that in PTSD, emotional traumatic experience could modify visual processing already at the pre-attentive level (Hendler et al., 2003). Although this finding may appear counterintuitive, it is in fact compatible with the complexity of PTSD phenomenology. Symptoms of both avoidance and numbing symptoms prevent adequate processing of the trauma, thus sustaining the PTSD symptoms (Foa, Riggs, & Gershuny, 1995). Yet, these intriguing findings concur with evidence from the highly significant negative correlation we found between the N1m component and the total score of PDS-avoidance. Further, avoidance symptoms overlap significantly with symptoms of depression, a common co-morbid disorder of PTSD. Most notably, depression constitutes co-morbid condition with high prevalence rates in PTSD (Keane & Kaloupek, 1997), which could also ostensibly influence the amplified responses in the N1m time window for neutral pictures. This result is also consistent with the significant positive correlation we found between the total PDS-avoidance score and the depression score. Taken together, the correlation between N1m component and total avoidance score, and the correlation between N1m component and total depression score evoked by picture viewing in our study speculates that the resources available for processing emotional pictures in PTSD subjects were inhibited. It therefore appears that the key finding here would be that PTSD represents a state of central nervous system (CNS) sensitivity and that individuals with PTSD, when faced with emotional stimuli, enter a state of protective inhibition in which the CNS responses to high arousing stimuli are dampened down to render them more tolerable (Paige et al., 1990). Furthermore, it is as yet an open question whether the sensitivity seen in PTSD subjects at early stages in visual processing may emanate from a lower neuronal threshold for automatic processing (Hendler et al., 2003).

Harnessing source space projection to the RMS approach may provide insights to the brain areas associated with affective picture modulation in PTSD patients. It will be important to relate the source space projection to affective picture processing in PTSD subjects, in schizophrenia subjects, and in control subjects using the minimum norm (Hamalainen & Ilmoniemi, 1994) procedure that estimates cortical sources. Within the framework suggested, future research may be able to elucidate which brain areas contribute to the processes of affective picture presentation and which neural basis underlies the experience and the expression of fear. Furthermore, distributed source models are intending to explain the measured signal in terms of brain generators, i.e. projecting the data into the source space (Grave de Peralta-Menendez & Gonzalez-Andino, 1998). They allow to include an unlimited number of sources in the source model i.e. the whole brain volume can be assumed to be possible active, though these sources cannot be estimated completely independent from each other and further restrictions on the solution must be applied (Hauk, Keil, Elbert, & Muller, 2002)

Chapter 4

Study III

Localizing cortical networks modulated by emotional arousal in PTSD

4.1 Summary

Brain imaging shows that selective attention to emotional picture content is accompanied by widespread activation in the human cortex. We used a linear estimation technique in a three-shell head model to determine spatially distributed patterns of brain activity associated with affective picture processing in PTSD patients, in schizophrenia patients and in control participants. Dipoles oriented tangentially to the shell surface were examined in three time intervals, roughly corresponding to N1m, early P3m and late P3m. As evidenced by the MNE, high arousing pictures elicited greater activity than low arousing (neutral) pictures did in PTSD patients over frontal and frontoparietal cortical networks for the early P3m window, over anterior and posterior parietal regions for the late P3m window and hereby representing differences among groups. There was evidence of failure in PTSD patients but not in schizophrenia patients to show a specific sensitivity to emotional modulation of visual cortex in the range of the N1m time window. Furthermore, source space projection from subsequent time windows such as early and late P3m revealed specific enhancement of electro-cortical activity in PTSD. This finding may reflect increased allocation of attentional resources to arousing stimuli over time in PTSD patients.

Keywords. Post-traumatic stress disorder, magnetoencephalography, affective picture processing, attention, source space projection, minimum norm estimate

4.2 Introduction

Brain regions implicated in affective picture processing in PTSD

Animal and human investigations of cerebral networks for emotional behavior have implicated the limbic system, primarily the amygdala, hypothalamus, and cortical regions including the orbitofrontal, dorsolateral prefrontal, temporal and parts of the parietal cortex (Adolphs et al., 1995; LeDoux, 1995).

Substantial insights into the nature of processes associated with brain responses to affective perception have come from studies of scalp-recorded event-related potentials (ERPs) in humans (Cacioppo & Gardner, 1999; Cuthbert et al., 2000; Keil et al., 2002). Central nervous correlates of affective picture processing have been investigated using a variety of recording techniques and experimental designs (Cuthbert et al., 2000; Keil et al., 2003; P. J. Lang, Bradley, Fitzsimmons et al., 1998).For example in an ERP study, Keil et al. found differential activity for emotional compared to neutral pictures at both of the P3 intervals. Sources of slow wave modulation were located in occipital and posterior parietal cortex, with a right-hemispheric dominance (Keil et al., 2002). As we noted earlier, ERPs as a dependent variable have shown that high arousing stimuli (pleasant or unpleasant) implicate a sustained late-positive wave, which is attenuated for less-arousing neutral images (Schupp et al., 2000). These findings point to a potential link between the sensitivity of these regions to stimulus emotionality and to their role in encoding information.

Neuroimaging techniques such as positron emission tomography (PET) and functional neuroimaging- particularly event related fMRI- have been used to map brain regions associated with the visual processing of emotional stimuli in healthy adults and thus have been valuable tools in identifying the neural sources of scalp recorded electric gradients.

In a study designed to investigate emotion-specific activation in visual cortex, fMRI revealed that functional activity was greater in occipital than in occipito-parietal regions when processing emotional pictures (pleasant or unpleasant) than when processing neutral pictures

(P. J. Lang, Bradley, Fitzsimmons et al., 1998). Evidence from a recent MEG study (Moratti et al., 2004) suggests that high arousing pictures (pleasant or unpleasant) elicited greater activity in frontoparietal cortical networks than low-arousing neutral pictures. Activation in the occipitotemporal regions showed a similar pattern but to a lesser extent than frontoparietal cortical regions, indicating that activity in higher-order frontoparietal cortical networks is modulated by emotional arousal. In addition, results from several imaging studies indicate that emotional content modulates brain activation in the visual cortex (H. Critchley et al., 2000; Lane et al., 1999; Taylor et al., 2000; Vuilleumier et al., 2001). Furthermore, structures outside of the limbic system also are activated during emotional processing of pictures and these responses are independent of the complexity of the images. Viewing affective pictures from the IAPS modulated occipital and occipital-temporal cortex activity relative to viewing non-aversive images (Taylor et al., 2003). Increased activity in the thalamus, hypothalamus, midbrain and medial prefrontal cortex is also associated with emotional processing of pictures from the IAPS (Lane, Reiman et al., 1997).

Consequently, converging evidence indicates that a widespread network of brain regions is involved in the variety of sub-processes associated with affective perception and behavior. The idea that afferent input from higher-order visual cortex and from prefrontal cortex modulates emotional processing would predict that there must be a mechanism for emotion-dependent changes in visual cortices.

Several brain regions have been implicated in affective picture processing in PTSD, leading some researchers to suggest that these regions represent a distributed network for affective picture processing. This network includes areas in the lateral prefrontal cortex, orbital prefrontal, anterior insular and anterior temporal cortex, temporoparietal cortex, and medial temporal areas (Bremner, 1999a; Bremner, Staib et al., 1999; Liberzon et al., 1999; Matsuo et al., 2003; Shin et al., 2001). Other areas implicated in affective picture processing include the amygdala (Rauch et al., 2000) and the cingulate gyrus (Semple et al., 2000).

Neuroimaging studies in PTSD have demonstrated that exposure to traumatic scripts resulted in (a) increased blood flow in limbic regions such as right amygdala, insula, orbitofrontal cortex, and anterior cingulate, and in (b) decreased blood flow in middle temporal and left inferior temporal cortex by utilizing positron emission tomography (PET; (Rauch et al., 2000). Evidence from another recent PET study during mental imagery in PTSD suggested that increased blood flow was implicated with activation in right amygdala and anterior cingulate, whereas decreased blood flow was implicated with activation in middle temporal and left inferior frontal cortex (Shin et al., 2001). Furthermore, symptom-provocation and cognitive activation studies using functioning neuroimaging provide further support for greater activation of the amygdala, anterior paralimbic structures, Broca's region and other neocortical regions and reduced activation of anterior cingulated cortex (ACC) in response to trauma-related stimuli in individuals with PTSD (Pitman et al., 2001; Shin et al., 2001; Villarreal & King, 2001). In one study, regional cerebral blood flow responses to trauma-related stimuli were examined in subjects with PTSD. Subjects were studied twice, while listening to combat sounds or white noise. Significant increases in the blood flow to the medial prefrontal cortex were observed in PTSD patients, but not in the control groups (matched combat exposed subjects without PTSD and healthy control subjects; (Zubieta et al., 1999). A few studies reported increased response in the prefrontal cortex (Bremner, Narayan et al., 1999; Zubieta et al., 1999). In another study, Bremner and colleagues reported no significant activation in ACC as well as decreased activation in ventral portions of ACC (subcallosal gyrus, Broadmann area 25) in PTSD (Bremner, Narayan et al., 1999; Bremner, Staib et al., 1999). Direct evidence for structural brain-associated differences of ACC in PTSD subjects comes from a study, in which the voxel-based morphometry showed a significant gray-matter volume reduction in the left ACC in trauma survivors with PTSD compared with those without PTSD (Yamasue et al., 2003). In another study, volumetric differences have also been demonstrated within the ACC and subcallosal cortex (SC) where the PTSD group (women with PTSD vs trauma-exposed women without PTSD) exhibited selectively decreased pregenual ACC and SC volumes (Rauch et al., 2003).

Taken together, the results of functional neuroimaging studies of the prefrontal cortex during trauma-related stimuli in PTSD are not yet conclusive. Several sources of evidence implicate regions in the prefrontal cortex and the higher order visual cortex as important components of the network that is sensitive to highly arousing emotional stimulation. These inconsistencies in the literature may arise from the differences in patient populations, the neuroimaging method, and the method and strength of trauma-related stimuli (Matsuo et al., 2003).

The present study seeks to elucidate which brain areas contribute to the process and which neural mechanisms underlie affective picture viewing among groups. Using a linear estimation technique in a three-shell head model we aimed at estimating the dipole strength of the visual evoked potential response and therefore to determine the sources of the neuromagnetic field.

4.3 Method

4.3.1 MNE and Nonparametric Permutation testing for Magnetoencephalography (MEG)

The main object of the MEG inverse problem is to reconstruct and localize the human brain electrical sources using magnetic field measurement outside the head. The signal recorded by a MEG sensor cannot be directly attributed to the underlying cortical region. The complex relationship between the signal detected by a sensor and an activated brain area is given by the solution of the forward problem (i.e., the calculation of the magnetic field generated by a point source). Given a set of MEG signals from an array of external sensors, the inverse problem involves estimation of the properties of the current sources within the brain that produced these signals.

Moreover, networks of cortical neural cell assemblies are the main generators of MEG signals. Large cortical pyramidal nerve cells are organized in macro-assemblies with their dendrites normally oriented to the local cortical surface. This spatial arrangement and the simultaneous activation of a large population of these cell assemblies contribute to the spatio-temporal superposition of the elemental activity of every cell, resulting in a current flow that generates detectable MEG signals (Baillet et al., 2001; Elbert, 1998).

To localize the electric sources inside the brain, various source assumptions and reconstruction techniques have been proposed (Baillet et al., 2001). Among them, the distributed source model with minimum-norm estimation (MNE) has been widely studied since Hämäläinen and Ilmoniemi first suggested this approach (Hamalainen & Ilmoniemi, 1984, 1994). Distributed source models are intended to explain the measured signal in terms of brain generators, i.e. projecting the data into the source space (Grave de Peralta-Menendez & Gonzalez-Andino, 1998). They allow the inclusion of an unlimited number of sources in the source model i.e. the whole brain volume can be assumed to be potentially active, though these sources cannot be estimated completely independent from each other and further restrictions on the solution must be applied (Hauk et al., 2002).

Of special interest for routine data analyses are the linear estimation techniques. The aim of the linear estimation procedures is to estimate brain activity by multiplying the magnetic field strength data at some sensor location at time **t** by a weighting vector, which should maximally correlate with the topography of one dipole of interest or, minimally with those of all other dipoles (Hauk et al., 2002; Keil et al., 2002). The inverse problem of magnetoencephalography suggests that a linear combination of magnetometer lead fields should be applied as an estimate for primary-current distribution in the brain (Hamalainen & Ilmoniemi, 1994).

In the present study source space projection was performed using a minimum norm procedure, first proposed by Hämäläinen and Illoniemi in a technical report (Hamalainen &

Ilmoniemi, 1984), that estimates the sources of the neuromagnetic field. Here we used the implementation suggested by Hauk et al. (2002), employing in-house software written in MATLAB^{TM}. The origin of the signal is estimated by performing multiple model dipoles, each being equidistantly arranged on three concentric shells, as a rough approximation of the brain volume. The current estimates are calculated in a grid with typically 5-7 mm spacing between source space points on the cortex. One issue concerning the MN procedure is that it generates a much larger number of solution points than data points (Hauk et al., 2002). For MEG analysis this can be addressed by selecting one shell from the three-dimensional source space (radii of solution shells are 0.8 for shell 1, 0.6 for shell 2, and 0.4 for shell 3) (Hauk, Berg, & Wienbruch, 1999a). In addition, an inverse solution is ascertained for these shells. Estimates of the minimum norm procedure for deep sources are not independent from superficial ones however, which can be seen as a further constraint imposed by the bio-electromagnetic inverse problem.

Another issue with regard to the MN approach directs that of depth sensitivity and spatial resolution among shells. Moreover, a significant difference between shells is that shell 1 as the most superficial shell has the best spatial resolution whereas shell 3 deepest has the worst. The opposite is true for depth sensitivity (Hauk et al., 2002). Our source model consisted of a three spherical volumes (see above), of which we used the outermost shell with radius of 8 cm around the center of the electrode array.

4.3.2 Linear Estimation Technique

The aim of the linear estimation techniques is to find a vector **j** such that multiplying it with the obtained data reveals a meaningful estimate for some property of the current distribution (Fell, Hauk, & Hinrichs, 2000). The relationship between magnetic fields measured at discrete points on or above the scalp surface is linear (Sarvas, 1987) where the expression of this equation can be written as:

$$\mathbf{d} = \int \mathbf{L}(\vec{r})\vec{j}(\vec{r})d\vec{r} + \varepsilon \qquad \text{Equation (4.1)}$$

where **d** is the data vector of measured data points and $\vec{j}(\vec{r})$ is the source current density. The data vector **d** which contains the recorded magnetic field strength at given sensors and which can be described as the product of the discrete lead field matrix **L**. The lead field matrix **L** can be represented as the sensitivity of every sensor to the sources located, as relating point sources to sensors (Hamalainen, Hari, Ilmoniemi, Knuutila, & Lounasmaa, 1993), and as the source current density vector **j** of these sources plus a random noise term ε (Grave de Peralta-Menendez, Hauk, Gonzalez-Andino, Vogt, & Michel, 1997).

$$\mathbf{d} = \mathbf{L}j + \varepsilon \qquad \text{Equation (4.2)}$$

In a mathematical framework the minimum norm estimate for **j** is the unique solution of the equation that assumes that the total length of the vector that represents the best fitting dipoles is minimized (see Equation 3). In other words, the MN procedure generates an estimate of **j**, which explains most of the data vector **d** and minimizes the sum of the currents **j** with respect to the focal ℓ_2 minimum-norm method. This means that the corresponding solution has the smallest ℓ_2 norm among all possible solutions.

Moreover, in attempts to minimize the strength (length) of the solution vector, the MNE tends to find solutions with the dipoles closer to the sensors (Stroink, Moshage, & Achenbach, 1998). The basic idea of MNE is, since **L** and **d** are known and ε is treated as if to be estimated with an acceptable accuracy, that we search for an estimate **j** by multiplying the pseudo-inverse of the lead-field matrix **L** (i.e., the sensitivity of the sensors to the sources) with the obtained data; when there are more sensors than mesh-points, i.e., M<N, where M, is the number of sensors and N, is the number of mesh-points, the model is underdetermined.

$$j^2 = \min \qquad \text{Equation (4.3)}$$

To this end, the lead field matrix **L** was computed for each subject of the groups, based on information on the center of a fitted sphere to the digitized head-shape, and to the positions of the MEG sensors relative to the head. A spheric shell was selected from the three-dimensional (3D) source space with evenly distributed 197 dipole locations. In the present study, dipoles were positioned on shell one (radius of solution shell was 0.8). Minimum Norm (MN) solutions were computed for distributions generated by dipoles tangential to the shell surface at radius 0.8. Moreover, the minimum norm can be calculated for any number and arrangement of sensors which suggests that it is not necessary to cover the whole source area (Hamalainen & Ilmoniemi, 1994).

4.3.3 Nonparametric Permutation Tests

Multichannel MEG recording has expanded manifold the amount of data recorded from each subject, and has led to problems of statistical inference. Given the high number of sensors, it was desirable, therefore, to apply a method that allows statistical inference and making some kind of correction for multiple comparisons. For correct statistical inference, the number of variables must somehow be reduced. In the case of a Bonferroni correction however, this is done by determining the desired threshold (e.g., 0.05). However the cost of a Bonferroni correction is high, since it increases the likelihood of Type II errors (accepting the null hypothesis when it is false). Nevertheless, sensitive statistical methods for handling this multiple comparison problem have been proposed (Singh, Barnes, & Hillebrand, 2003). Whatever result is obtained with one method, there are still infinitely many more statistical methods such as multiple comparisons (Holmes, Blair, Watson, & Ford, 1996) and random effects that have been assessed for volumetric functional neuroimaging techniques, such as fMRI (Friston, Holmes, Worsley, Poline, & Frith, 1995; Poline, Worsley, Holmes, Frackowiak, & Friston, 1995) and PET (Shaw et al., 2002). Furthermore, random effects analyses are often not possible due to small number of subjects, making it difficult therefore to perform robust between-group univariate analyses (Shaw et al., 2002). As an alternative, therefore, we implemented non-parametric permutation methods, which have been suggested and applied by several authors for use in functional neuroimaging (Arndt et al., 1996; Brammer et al., 1997; Holmes et al., 1996). In one case, Singh et al. (Singh et al., 2003) showed that permutation testing can be applied to assess statistical significance by investigating the neuronal sources from the MEG signal.

Based on these findings, an implementation of the permutation test was introduced. The procedure was as follows: In a first step, we calculated the F-value for trend analysis for repeated measures factors with the within-subjects factors being *affective category* [3 conditions: pleasant vs. neutral vs. unpleasant] and *time windows* [N1m, early P3m, late P3m] on waveforms and for each subject. The matrix **x** represented the data array arranged in such a way that sensors were represented as rows, subjects as columns and condition in the third dimension. Conditions were arranged in such a way that they corresponded to the trend. Since an a priori hypothesis existed, linear contrast analysis statistics were applied for further analysis. The weights for orthogonal contrasts (quadratic, in the present study) always had to sum up to zero (quadratic trend [1, –2, 1]), as has been suggested by Rosenthal and Rosnow (Rosenthal & Rosnow, 1985). In a next step for each permutation iteration we calculated the critical values for each group resulting in critical F-values [in PTSD patients, (6.92), in schizophrenia patients (7.04), and in control subjects (7.12)]. This method yields an F- (here critical F at 0.05 significance level) and an effect-size value $r_{contrast}$. This conservative threshold for activation was chosen to achieve acceptable control over type I error. The F maps were thresholded at $P < 0.05$. Generically all conditions for all time series were plotted in histograms where sensors with critical F values corresponding to each group were identified (Figures, 4.1, 4.2, 4.3).

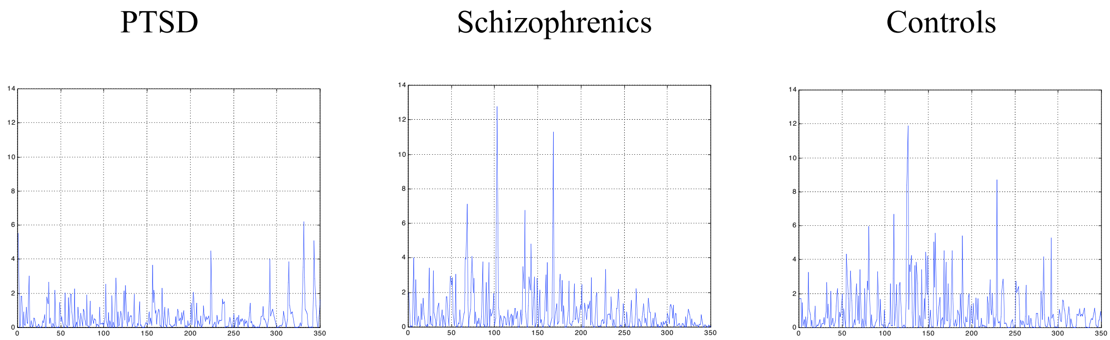

Figure 4.1: Graphical representation of histograms where sensors with critical F values corresponding to each group (PTSD, Schizophrenics, Controls) where identified for the N1m deflection.

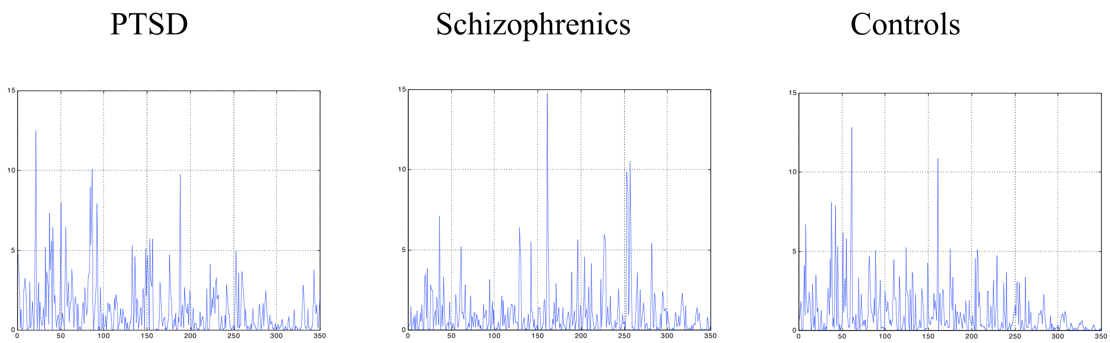

Figure 4.2: Graphical representation of histograms where sensors with critical F values corresponding to each group (PTSD, Schizophrenics, Controls) where identified for the early P3m deflection.

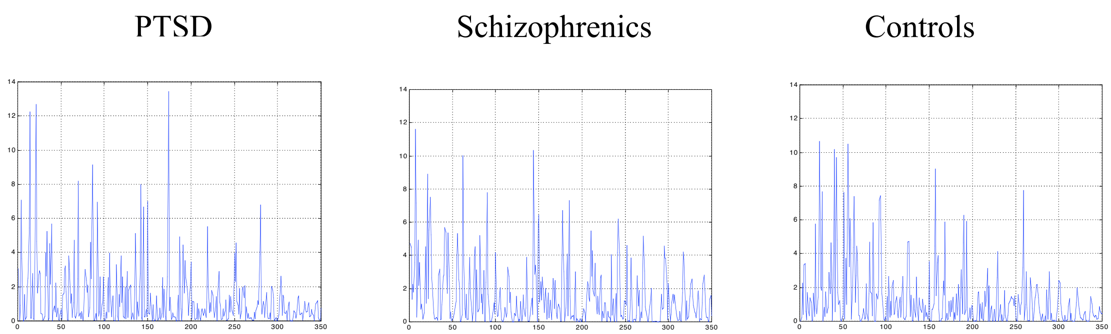

Figure 4.3: Graphical representation of histograms where sensors with critical F values corresponding to each group (PTSD, Schizophrenics, Controls) where identified for the late P3m deflection.

4.3.4 Mapping of statistical parameters

After appropriate preprocessing (see A. *Linear estimation technique*) of the datasets, contrast analysis for a quadratic trend was performed for each of the 197 dipoles and the F values were projected on the same shell as used by the MNE procedure. Mapping of statistical parameters was therefore conducted to test the hypothesis that high arousing pictures (pleasant and unpleasant versus neutral) generate greater dipole strength in PTSD patients than in schizophrenia and in control subjects. Moreover, activated dipoles were then plotted and were superimposed on a colored scale in the MATLAB^{TM} software, to create F-contrast brain maps. Colors in the figures represent node numbers. The different panels depict different views of the MNE shell containing dipole locations where F values are projected on for the N1m, early, and late P3m deflection for the difference pleasant and unpleasant vs. neutral (Figures, 4.12, 4.13, 4.14).

4.3.5 Statistical analysis

For the purpose of statistical analysis and for assessing effects of picture content on estimated source parameters of magnetocortical activity, we conducted the same statistical analysis as mentioned in Chapter 3 for dipole strengths estimated using the minimum norm procedure. That is, the 350 dipoles on the shell were pooled into regional means for each hemisphere (left, right), for region (anterior, posterior), for each affective category (pleasant, neutral, unpleasant) and for time series. This resulted in three time windows, which were chosen on the basis of the significance level exhibited by calculating the root mean square field strength from the sensors that covered the field pattern of the particular component (see chapter 3). In this case dipole strengths in these regions were assessed in three time windows, corresponding roughly to N1m(140-220 ms), early P3m(250-340 ms), and late P3m(350-490 ms). These data were submitted to repeated-measures analysis of variance (ANOVA) with one between-subject factor (3 levels: PTSD patients, schizophrenia patients, and control participants) and three within-subject factors affective category (3 levels: pleasant, neutral, unpleasant), hemisphere (2 levels: left, right), and region (2 levels: anterior, posterior). In the case of significant results ($P < 0.05$) of the ANOVA the Tukey-Kramer procedure was applied for post-hoc analysis. Significant interactions were clarified by either breaking them into simple main effects or by computing univariate F contrasts. The ANOVA's reported here required clusters of contiguous dipoles for each time window. Accordingly, early affective dipole strength processing was calculated in bilateral clusters as area measures in the time interval from 140-220 ms [left hemisphere dipoles: 68:70, 96:98, 127:129, 159:161], [right hemisphere dipoles: 74:76, 102:104, 134:136, 167:169], (as shown in the left panel of Figure 4.4). The early P3m affective processing time window was scored in the time interval from (250-340 ms) across left and right hemisphere anterior and posterior clusters of dipoles [left hemisphere anterior dipoles: 21:25, 40:45, 61:67, 90:96, 123:126], [left hemisphere posterior dipoles: 26:28, 46:48, 69:72, 97:101, 128:132], [right hemisphere anterior dipoles: 32:36, 52:57, 77:83, 106:112, 138:141] [right hemisphere posterior dipoles: 29:31, 49:51, 73:76, 101:104, 132:136] (as shown in left panel of Figure 4.4). The late P3m time window was calculated in the time interval from 350-490 ms in left and right anterior and posterior hemisphere clusters of dipoles [left hemisphere anterior dipoles: 10:12, 22:28, 40:47, 66:71], [left hemisphere posterior dipoles: 193:196, 226:228, 256:258, 283:286] [right hemisphere anterior dipoles: 16:18, 31:37, 51:58, 76:80], [right hemisphere posterior dipoles: 198:201, 230:232, 260:262, 287:290] (as shown in the right panel of Figure 4.4).

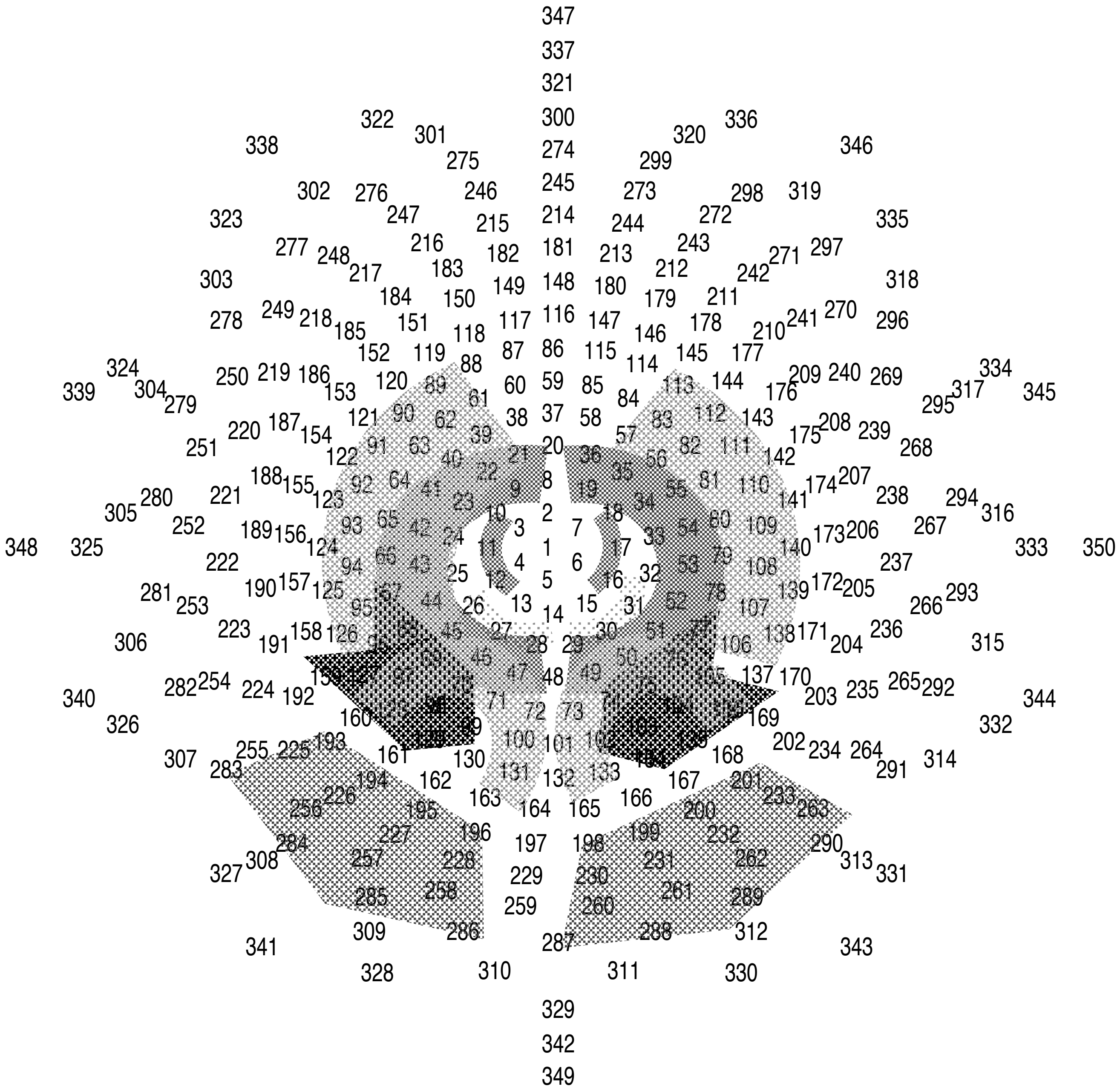

Figure 4.4: Selected clusters of contiguous dipoles for each time window (N1m, early P3m, late P3m).

4.4 Results

4.4.1 Minimum Norm Estimate

N1m time window

Dipole strength was affected by picture content in the N1m time window, [F(2, 30) = 3.4, $p < 0.03$, □= .96] reflecting greater dipole strength for emotive pictures [either pleasant: .42 ± .2 nA/cm^2, or unpleasant: .41 ± .2 nA/cm^2 as compared to neutral pictures: .39 ± .2 nA/cm^2] (Figure 4.5). The calculation of follow-up tests indicated enhanced dipole strength when viewing pleasant pictures, compared to neutral [Tukey-Kramer $p < 0.05$] whereas other differences did not reach significance.

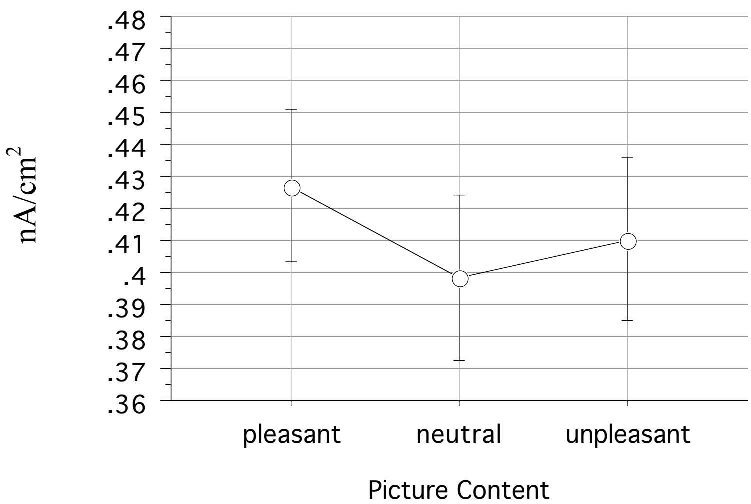

Figure 4.5: Graphical representation of effects of picture content (pleasant, neutral, unpleasant) on minimum norm dipole strength for the N1m time window. Error bars represent standard errors

During the N1m time window (140-220 ms) the main effect of Hemisphere approached statistical significant and indicated that the visual stimulation elicited most activity over the right hemisphere as compared to left hemisphere [F(2, 20) = 5.0, $p < 0.03$, □ = .21]. Follow-up tests demonstrated that effects were restricted to the right hemisphere [Tukey-Kramer $p < 0.05$ for the comparison left and right hemisphere; mean dipole strength for left hemisphere: .38 ± .2 nA/cm^2, mean dipole strength for right hemisphere: .4 ± .2 nA/cm^2].

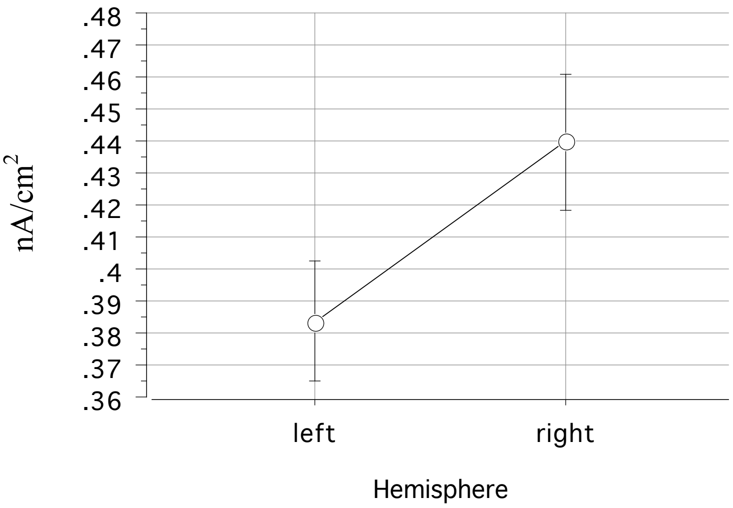

Figure 4.6: Graphical representation of effects of Hemisphere on minimum norm dipole strength for the N1m time window. Error bars represent standard errors.

A Hemisphere by Picture Content and Group interactions demonstrated that effects of picture content differed across Hemispheres and for Group [F(4, 60) = 3.0, $p < 0.02$, □= .60] (Figure 4.7). Follow-up comparisons showed that the PTSD patients exhibited a picture content effect indicating that pleasant and unpleasant pictures were generally associated with greater dipole strength than were neutral pictures, $p < 0.05$ in left hemisphere [Tukey-Kramer for pleasant and unpleasant pictures only, $p < 0.05$,] and a quadratic trend in PTSD patients for picture content [F(1,11) = 5.8, $P < 0.04$] and a quadratic trend in schizophrenia patients for the interaction Hemisphere by Picture Content [(1,11) = 7, $P < 0.02$]. Post-hoc testing in schizophrenia patients revealed a right hemisphere sources restriction in discriminating between emotional (pleasant or unpleasant) and neutral pictures, $p < 0.05$. In control participants effects differed across hemispheres, indicating differences with respect to source distribution rather than in source strength [Tukey-Kramer $p < 0.05$]. There was no difference among groups.

No interaction involving region was found for the N1m time window. Paralleling the RMS data, no significant main effects or interactions involving picture content were found in the P2m window.

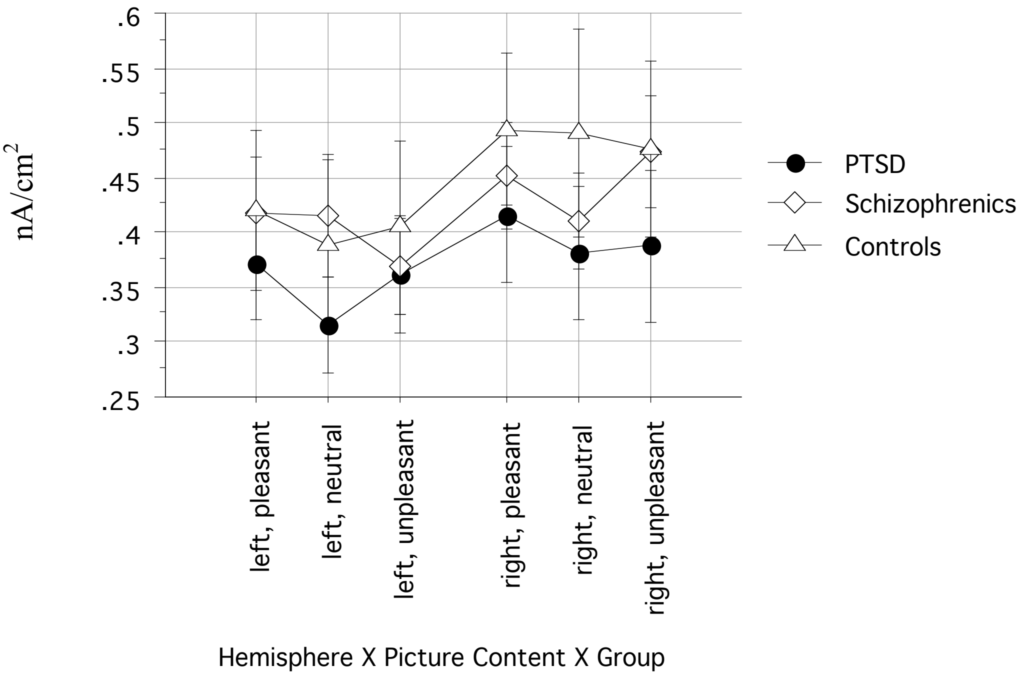

Figure 4.7: Graphical representation of effects of Hemisphere by Picture Content by Group on minimum norm dipole strength for the N1m time window. Error bars represent standard errors.

Early P3m time window

In the early P3m window, a main effect of region indicated that over the anterior regions effects were significant higher when compared to posterior regions [$F(1, 30) = 22.9$, $p < 0.001$, = .84] (Figure 4.8). This difference was also seen in post-hoc testing where anterior regions sources exhibited enhanced activation [Tukey-Kramer $p < 0.05$ for the comparison between anterior and posterior regions].

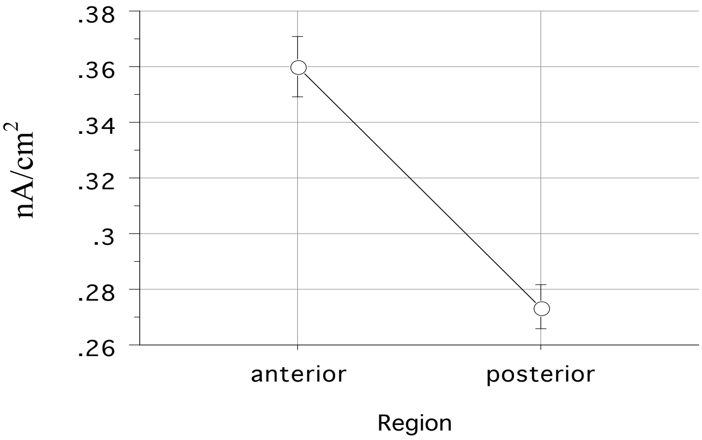

Figure 4.8: Graphical representation of effects of region on minimum norm dipole strength for the early P3m time window. Error bars represent standard errors.

An interaction involving Picture Content by Region (anterior-posterior region) [$F(2, 60) = 3.9$, $p < 0.03$, □=.80] indicated that effects of emotionality effect where somewhat stronger in the anterior than in the posterior regions (Figure 4.9). Post-hoc testing demonstrated that effects were restricted to the anterior regions [Tukey-Kramer $p < 0.05$] whereas picture content differences did not reach significance.

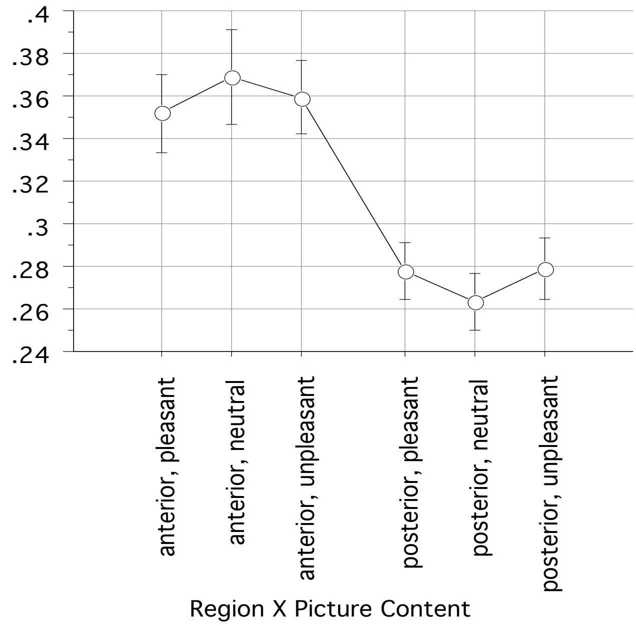

Figure 4.9: Graphical representation of effects of region by picture content on minimum norm dipole strength for the early P3m time window. Error bars represent standard errors.

In addition, there was also a significant Hemisphere by Region by Picture Content by Group interaction [$F(4, 60) = 3.3$, $p < 0.02$, = .76] indicating that across hemispheres greater dipole strength was more pronounced for anterior regions [Tukey-Kramer $p < 0.05$ for comparisons between anterior and posterior regions] whereas these region effects where more pronounced for PTSD patients [Tukey-Kramer $p < 0.05$ for comparisons between anterior and posterior regions] and for the schizophrenia patients [Tukey-Kramer $p < 0.05$ for comparisons between anterior and posterior regions] (Figure 4.10). No effects involving picture content and hemisphere were significant.

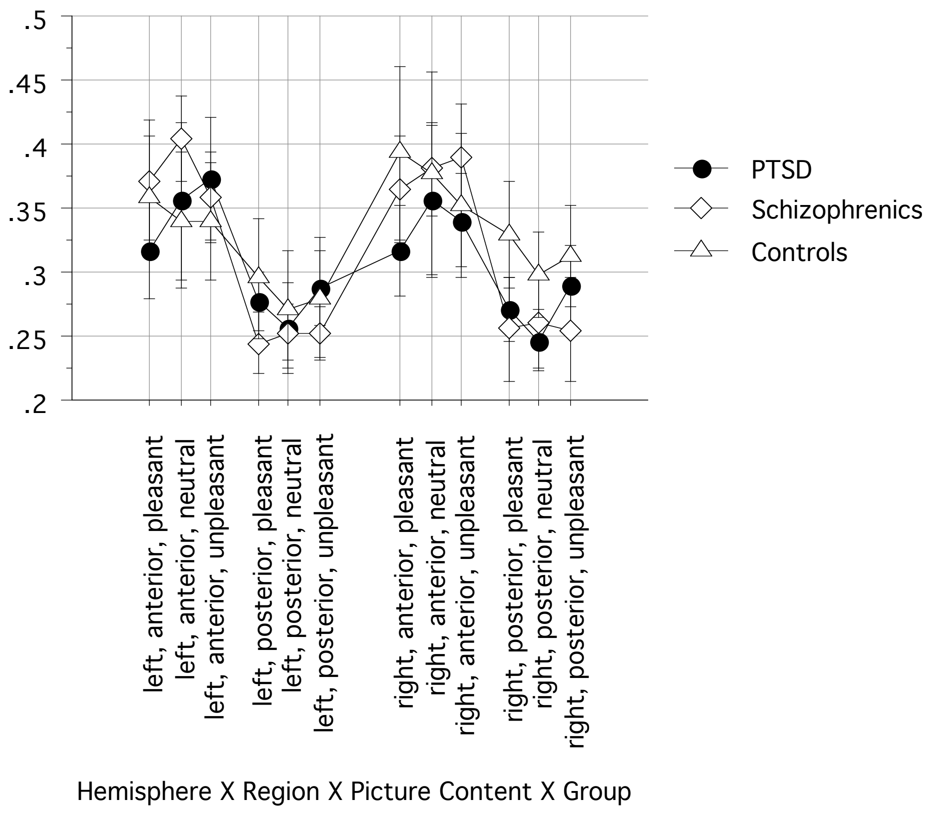

Figure 4.10: Graphical representation of effects of hemisphere by region by picture content by group on minimum norm dipole strength for the early P3m time window. Error bars represent standard errors.

Late P3m time window

ANOVAs in the late P3m window exhibited that the late P3m was modulated as a function of picture content indicating enhanced dipole strength [$F(2,30) = 8.2$, $p < 0.0001$, □= .96] (Figure 4.11). This trend was evident regardless of group and was characterized by an enhancement of dipole strength by pleasant [.26 ± .1 nA/cm^2] and unpleasant pictures [.28 ± .1 nA/cm^2] as compared to neutral pictures [.24 ± .1 nA/cm^2]. Follow-up comparisons demonstrated that pleasant and unpleasant pictures elicited enlarged dipole strengths as compared to neutral pictures [Tukey-Kramer $p < 0.05$ for comparisons between pleasant, neutral pictures and unpleasant, neutral pictures]. No interaction involving region or hemisphere was found, indicating that contents differed with respect to source strength rather than chances in source distribution. In addition, although there was no interaction involving the between-subject factor Group, the enhancement on dipoles strength for pleasant and unpleasant pictures across hemispheres was more pronounced for PTSD patients compared to schizophrenia patients and control participants.

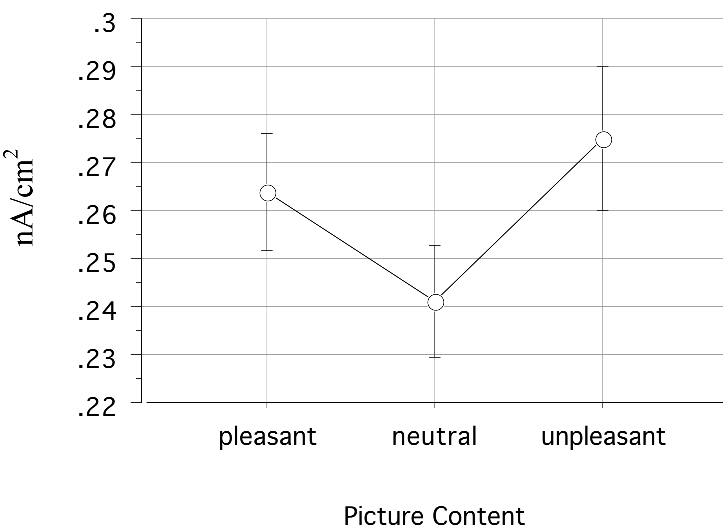

Figure 4.11: Graphical representation of effects of picture content on minimum norm dipole strength for the late P3m time window. Error bars represent standard errors.

4.4.2 Contrast Maps –Analysis of the topographical specificity

N1m time window

To determine how the effects of emotional pictures (arousal) were processed in the different time windows and for different groups (PTSD patients, schizophrenia patients and control participants), and to elucidate which cortical areas contribute to affective picture processing, we calculated F-contrast maps throughout all the dipoles of the minimum norm shell. Statistical contrast maps displayed in colored scaled according to significance, were used to identify loci of significant signal chance.

Plotting statistical parameters in the N1m time window revealed that the quadratic trend maps comparing activation among groups for emotional (pleasant and unpleasant) to that for neutral pictures were greatest for PTSD patients at right inferior occipital dipole sites, whereas for schizophrenia patients F values were greater at superior occipito-parietal dipole sites in the right hemisphere. In addition, F values were greatest for control participants at posterior temporal dipole sites with a left hemispheric predominance (Figure 4.12).

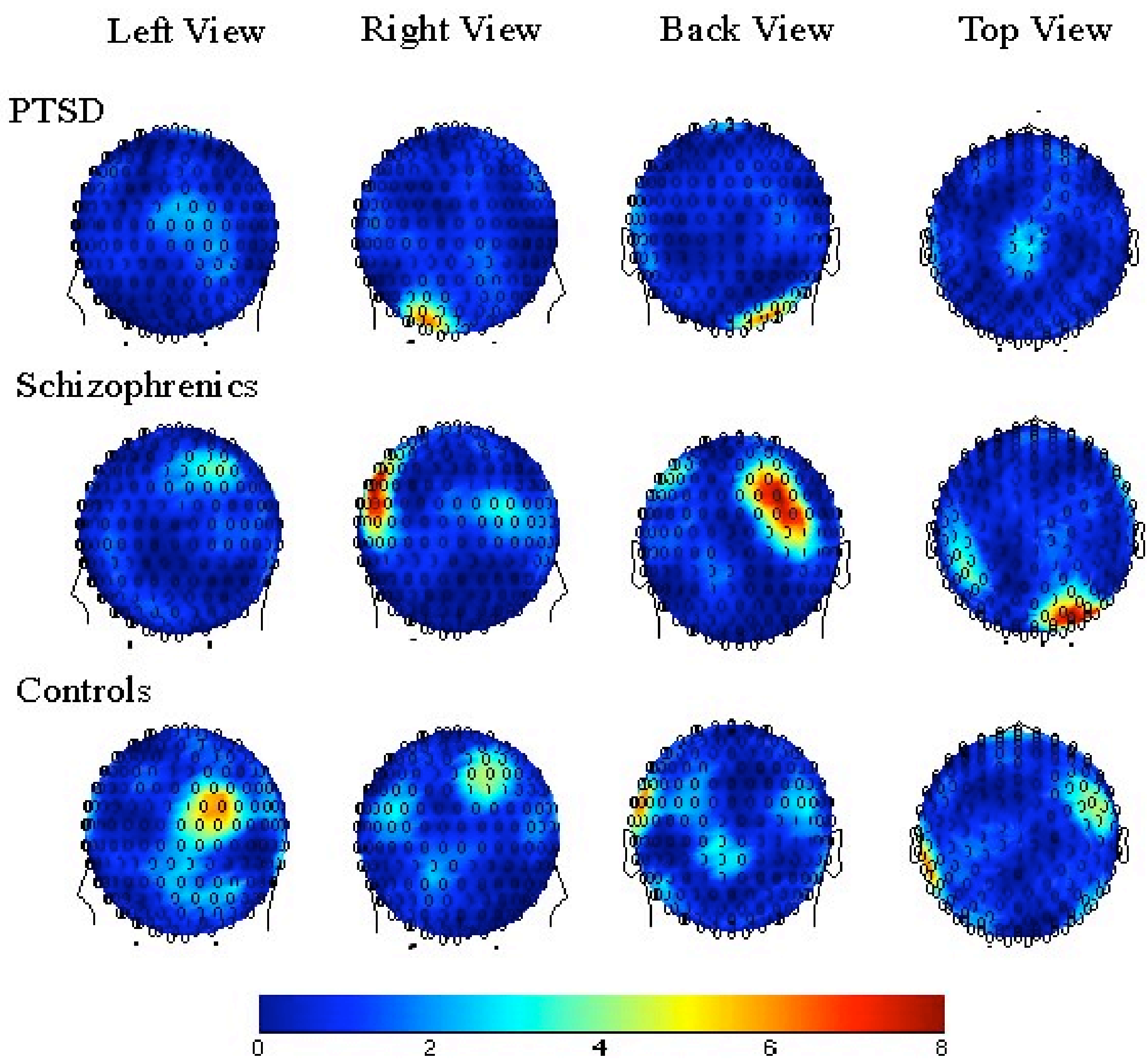

Figure 4.12: Mapping of statistical parameters. The color bar indicates the F value level. The different panels depict different views of the MNE shell containing dipole locations where F values are projected on for the N1m deflection for the difference pleasant and unpleasant vs. neutral among groups. Colors in the figures represent node numbers.

Early P3m time window

In the early P3m time window contrast maps revealed that the quadratic trend for the effects of emotional stimulus presentation (pleasant and unpleasant versus neutral) involved in PTSD patients fronto-parietal dipole sites with a left hemispheric dominance for inferior and superior dipole sites. In schizophrenia patients early P3m time window contrast maps revealed that the quadratic trend comparing activation for emotional (pleasant and unpleasant) to that for neutral pictures was at posterior parieto-occipital dipole sites. Particular dipole sites in control subjects involved in processing emotional (pleasant and unpleasant) pictures as compared with neutral pictures, as revealed by contrast maps, included bilateral superior temporo-parietal dipole sites. Secondary dipole sites in control participants that were also generally involved in processing for emotional pictures were in the right inferior occipital dipole sites (Figure 4.13).

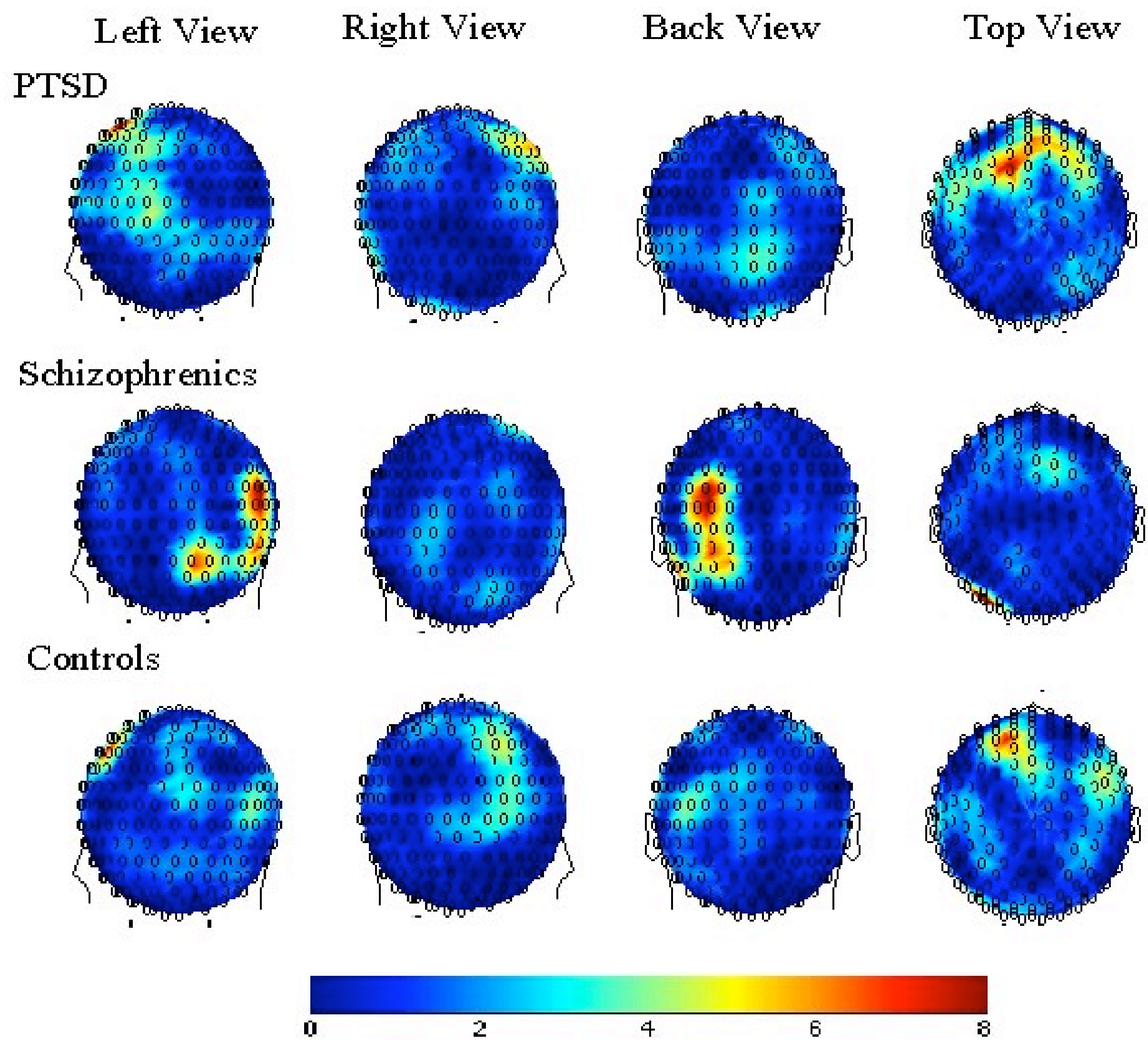

Figure 4.13: Mapping of statistical parameters. The color bar indicates the F value level. The different panels depict different views of the MNE shell containing dipole locations where F values are projected on for the early P3m deflection for the difference pleasant and unpleasant vs. neutral among groups. Colors in the figures represent node numbers.

Late P3m time window

Mapping the quadratic trend for the late P3m window comparing activation for emotional (pleasant and unpleasant) to that for neutral pictures among groups, revealed that the modulation of source strength as a function of arousal was more pronounced in PTSD patients in the left hemisphere than the right hemisphere and larger in the superior than in the inferior parietal dipole sites. As can be seen in Figure 4.14, an additional cluster of F values in PTSD patients was found in right temporal dipole sites.

Quadratic trend maps in schizophrenia patients indicated that emotionality effects were stronger in bilateral superior parietal dipole sites, with predominance on the right hemisphere. A secondary area that was also generally involved in high arousing picture processing in schizophrenia patients included inferior temporal dipole sites with a right hemispheric dominance.

In control participants, a cluster of particular dipole sites involved in processing of emotional (pleasant and unpleasant) pictures, as compared with neutral pictures, including stronger activity in superior temporal dipole sites than inferior dipole sites in the left hemisphere. Furthermore, a secondary area that was also generally involved in high arousing picture processing in control participants included superior temporal dipole sites in the right hemisphere, although activity was weaker for these regions (Figure 4.14)

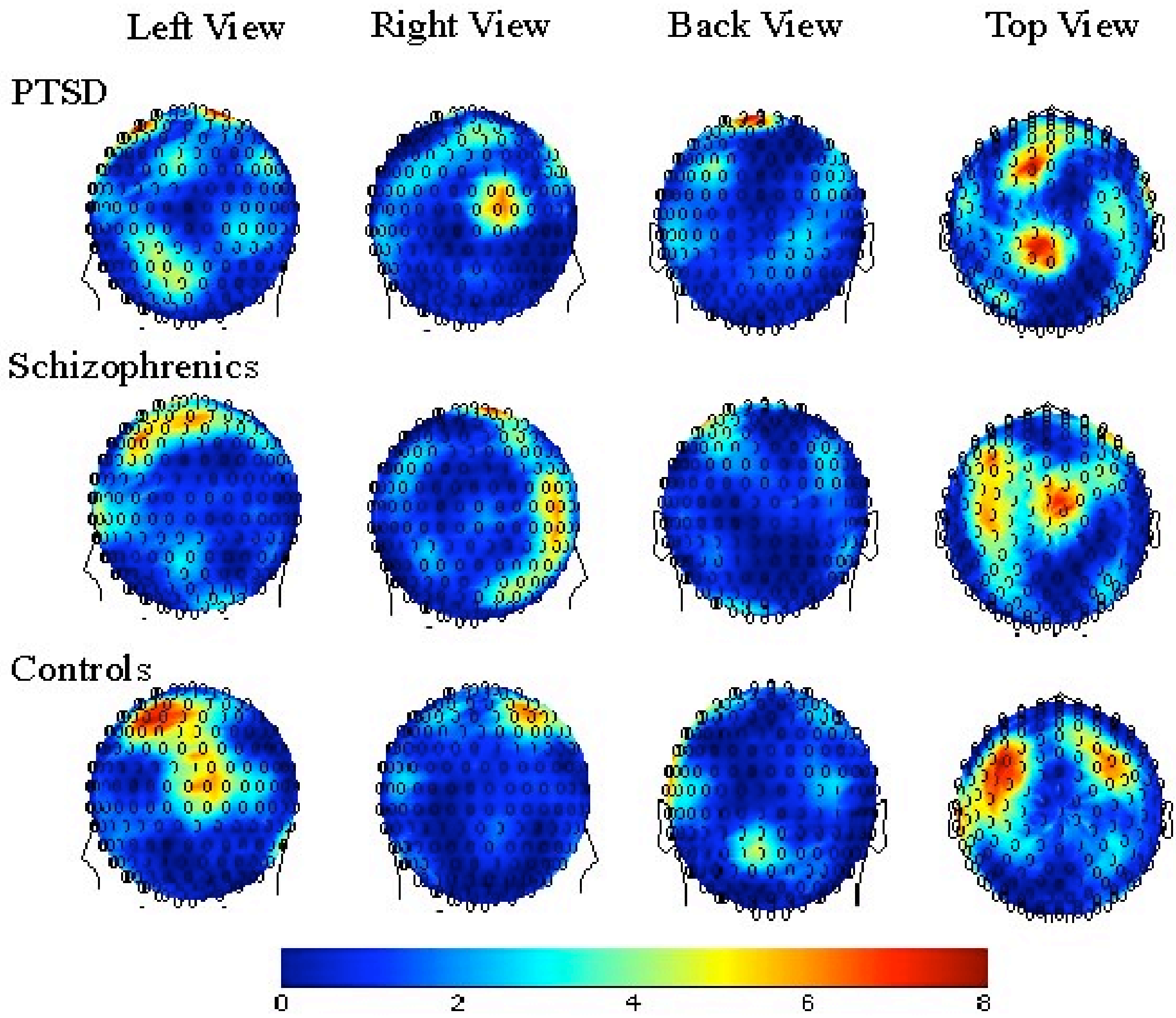

Figure 4.14: Mapping of statistical parameters. The color bar indicates the F value level. The different panels depict different views of the MNE shell containing dipole locations where F values are projected on for the late P3m deflection for the difference pleasant and unpleasant vs. neutral among groups. Colors in the figures represent node numbers.

4.5 Discussion

There is a convergence of evidence from neuropsychological, psychophysiological, and neuroimaging studies that mental processes such as visual processing of emotional stimuli are associated with a fast network of distributed brain regions. Magnetoencepalography -with its combination of a high resolution in time and a relatively good resolution in space- offers a powerful method to investigate the cerebral substrates of such processes (Keightley et al., 2003).

In support of the idea that the processing of emotional visual stimuli recruits a number of brain areas, the present study aimed at assessing group differences when affective information is presented to torture victims, to schizophrenia inpatients and to healthy participants using MEG and a distributed source modeling technique. The goal of source analysis was twofold: (1) to elucidate possible brain regions involved in processing emotional (pleasant or unpleasant), as compared with neutral, pictures, and (2) to determine the topographical specificity using contrast maps for each condition. Therefore, in this study we incorporated nonparametric permutation testing in order to assess the statistical significance in the analysis of MEG data.

Using a high number of MEG-sensors, effects of emotional content were strongest in posterior sites, near occipital-temporal cortex, prefrontal cortex and posterior parietal cortex. As found in previous studies, differences in the magnitude of positive-going dipole strength in time windows later than 300 ms were found as function of emotional arousal (Cuthbert et al., 2000; Keil et al., 2002; Schupp et al., 2000). Examining the differences among groups between affective contents in terms of dipole strength in three time windows, we found no stable hemispheric asymmetry but changing preponderance over the course of time among groups.

Effects of emotional content on the N1m component

Mapping of statistical parameters indicated that the modulation of the source strength as a function of emotional arousal was in earliest time window (N1) over right posterior occipital dipole sites in PTSD patients. Nonetheless, lack of content specificity point to a possible sensitivity of the visual cortex for processing high arousing stimuli in PTSD for the earliest time window. The PTSD patients showed very marginal influences on emotional content on the visual cortex, suggesting little involvement of the occipital visual dipole sites within this network of regions. A greater response over the occipito-parietal dipole sites for processing high arousing stimuli was seen in schizophrenia patients for the early N1m time window suggesting that basic visual areas were activated. A number of studies on cerebral processing using mangetoencephalography and EEG specifically related to faces have provided evidence that it might begin as early as about 110-130 ms after stimulus onset in occipital brain structures (Halgren, Raij, Marinkovic, Jousmaki, & Hari, 2000; Streit, Ioannides et al., 2001). Healthy controls exhibited a differential hemispheric activity displaying more activity over the left hemisphere at posterior temporal dipole sites.

As discussed in Chapter 3, it could be claimed that the decreased activation found in PTSD patients for high arousing pictures over posterior occipital dipole sites, posits a failure of PTSD patients to process stimulus context at the pre-attentive level (Felmingham et al., 2002). For instance, PTSD subjects revealed reduced sensory gating (Neylan et al., 1999) and increased mismatch negativity (Morgan & Grillon, 1999) to neutral auditory stimuli.

One explanation for this could be that PTSD is characterized by a lower neuronal threshold for automatic emotional processing (Hendler et al., 2003). This view is supported by evidence from a previous ERP study where unattended trauma-related stimuli evoked a similar response to attended non-trauma related stimuli (Bleich et al., 1996). In the same vein, evidence from several studies demonstrated a trauma-related bias of the stroop- response in PTSD (Bryant & Harvey, 1997; Foa et al., 1995; MacLeod & Hagan, 1992). Another ERP study have demonstrated that PTSD patients failed to differentiate between neutral and angry expressions for the early (N110) components over posterior temporo-occipital regions, and had reduced ERP responses compared to controls (Felmingham et al., 2003). The authors suggested that the PTSD group might have had difficulty discriminating generalized threat and non-threatening stimuli.

Furthermore, we must emphasize here the existence perhaps of dissociable networks for emotional versus non-emotional pictures in PTSD patients. This finding converges with results from another study suggesting that hyper-responsivity within the higher order visual cortical areas to high arousing stimuli is purportedly exacerbated by (or possibly caused by) insufficient top-down inhibition from occipital cortical regions (Rauch et al., 2003).

Based on this evidence, and our finding of failure in PTSD patients to show a specific sensitivity to emotional modulation of visual cortex in the range of the N1m time window, we may speculate that PTSD patients exhibit for the early time windows a bias towards emotional modulation. It has been proposed that an impairment in emotional modulation and gating function may underlie the neurobiology of PTSD (Hamner, Lorberbaum, & George, 1999).

The patterns of input into visual cortex during emotional modulation differ greatly among PTSD subjects and schizophrenia inpatients and control subjects, suggesting differential modulation of affective picture processing among groups. Emotional modulation of the visual cortex has been widely described in conditions of externally presented emotional stimuli (Adolphs, 2002; H. Critchley et al., 2000; Rotshtein, Malach, Hadar, Graif, & Hendler, 2001; Taylor et al., 1998), possibly mediated by the amygdala (Rotshtein et al., 2001). The fact that in PTSD patients this path became less activated during affective picture processing might be related to the highly reported avoidance scores that are a hallmark of PTSD and may reflect a maladaptive response to environmental threat (LeDoux, 1996).

Effects of emotional content on the early P3m component

The activations that differentiated groups by dipole strength showed a consistent evolution in time among groups. As illustrated in the statistical parametric maps of estimated dipole strength, content effects among groups differed dramatically. Arousal related modulations were observed in PTSD patients for the early P3m window over prefrontal frontoparietal regions with a left hemispheric dominance. The source areas of these effects were located with greatest activity over frontoparietal dipole sites for left hemisphere. Schizophrenia inpatients exhibited enhanced dipole strength over higher order visual cortical areas with a left hemispheric dominance. By contrast, schizophrenic patients exhibited a distinct failure to activate prefrontal and frontoparietal cortical areas. This suggests, that the circuitry recruited to process affective pictures for later latencies in schizophrenia inpatients was restricted in occipital areas. We may speculate that these findings support the notions of impaired emotional processing in schizophrenia inpatients (Gur et al., 2002; Phillips et al., 1999; Schneider et al., 1998; Streit, Ioannides et al., 2001). In addition, criminal psychopaths showed structural abnormalities (reduced grey-to white-matter ratio) in the prefrontal cortex and abnormal activation of the orbitofrontal cortex (Raine, Lencz, Bihrle, LaCasse, & Colletti, 2000) and the amygdala in functioning imaging studies (Kiehl et al., 2001), together with reduced autonomic emotional responsivity. Control participants showed enhanced dipole strength over fronto-parietal dipole sites for left hemisphere and over temporo-parietal dipole sites for the right hemisphere but to a lesser extent as compared to PTSD patients.

It seems that in PTSD patients affective modulation is processed differently as compared to schizophrenia inpatients and control subjects at the sensory level (Hendler et al., 2003). This difference in sensory processing of the affective modulation could well be linked to a predisposed mechanism in PTSD patients. Several studies have implicated frontal cortical areas modulating emotional responsiveness in PTSD patients (Vermetten & Bremner, 2002). Thus, the absence of activation in prefrontal regions in both groups' schizophrenia inpatients and control subjects is consistent with the conclusion that the activation of these cortical areas in PTSD patients could be a specific response. Recent results of functional neuroimaging studies of the prefrontal cortex during trauma-related stimuli in PTSD showed increases in the prefrontal cortex. Several studies have implicated this pathway in the processing of emotional material (Matsuo et al., 2003; Zubieta et al., 1999). The issue ties in with the role of these cerebral substrates in PTSD patients being involved in the regulation of arousal (Zubieta et al., 1999), given other lines of evidence suggesting that in studies using metabolic imaging techniques, the modulation of activity at frontoparietal dipole sites elicited by the arousal dimension of emotional pictures demonstrate an involvement of specific cortical networks implicated in attention (Corbetta, 1998; Le, Pardo, & Hu, 1998; Rushworth, Paus, & Sipila, 2001) and orienting and maintaining the alert state (Fernandez-Duque & Posner, 2001).

In recent studies emotional challenges by films or the recall of emotional material were associated with increased function of this area (George et al., 1995; Lane et al., 1999; Reiman et al., 1997). Convergent evidence points to reciprocal connections between the amygdala and the ventral/medial prefrontal cortex. Rauch and colleagues proposed a model of PTSD emphasizing the amygdala and its interaction with limbing and paralimbing structures. According to this model amygdala hyper-responsivity to threat-related stimulus is perhaps exacerbated or due to inefficacy of top-down modulation by ventral/medial prefrontal cortex and hippocampus. These findings support an evolving neurobiological model of PTSD focusing on the interplay between these frontal cortical regions, the amygdala and the hippocampus.

Effects of emotional content on the late P3m component

Mapping of statistical parameters indicated that the modulation of dipole strength as a function of emotional arousal for the late P3m time window showed specific enhancement for emotional content in PTSD patients over frontal dipole sites and posterior parietal dipole sites with a left hemispheric preponderance. Such a modulation was also evident at temporal dipole sites with a right hemispheric predominance but to a much lesser extent. An enhancement of dipole strength in the late P3m time window was found for high arousing pictures in schizophrenia inpatients over right parietal and temporal dipole sites. Furthermore, a modulation by emotional arousal was observed in schizophrenia inpatients over left parietal dipole sites but to a lesser extent. A modulation for affective picture processing was observed in control subjects occurring in bilateral anterior sites associated with temporal cortex with greatest activity over left hemisphere. This finding is in line with studies that have implicated cerebral networks in healthy people that modulate emotion processing such as temporal and parts of the parietal cortex (Adolphs, Damasio, Tranel, & Damasio, 1996; LeDoux, 1995). However, the main difference among PTSD patients, schizophrenia patients and control participants with regard to the modulation of the source strength as a function of emotional arousal for the late P3m time window was due to increased activation in frontal and parietal dipole sites in PTSD patients. This suggest that the topography of amplitude modulations in PTSD patients involved regions that supported spatial and visual aspects of emotional processing at the prefrontal and parietal cortices (Wik et al., 1993).

Anatomical studies have reported that the posterior parietal cortex is one major source of top-down control of ventral stream areas (Hopfinger, Buonocore, & Mangun, 2000; Kastner, Pinsk, De Weerd, Desimone, & Ungerleider, 1999; Kastner & Ungerleider, 2001). Furthermore, neuroimaging studies in humans have shown activation of posterior parietal cortex, in many tasks that require top-down attentional control. It is suggested that the parietal cortex and prefrontal cortex are involved in visuo-spatial processing that is an important component in patients with PTSD. It is suggested that connections between the parietal and prefrontal cortex are required in order to permit the organism to rapidly and efficiently execute motor responses to threat (Vermetten & Bremner, 2002). Most interestingly, in our study only PTSD patients presented this network pattern and not the other two groups for the late P3m time window, which could be related as more characteristic of PTSD. In the current study, this would suggest that the increased reactivity seen in PTSD patients in the late P3m time window might reflect an involvement of regions that are activated both with pleasant and unpleasant pictures and thus may be involved in the arousal component of emotional response. In general, these findings point to a network of related regions, which are mobilized in patients with PTSD during emotional picture processing.

Conclusions

The evidence cited in this study highlights that the occurrence of an emotional stimulus elicits a cascade of neural responses that results in enhanced activation in specific brain areas. PTSD patients demonstrated enhanced dipole strengths over frontal and posterior parietal cortices for late latencies. These findings are consistent with a view suggesting that in PTSD, emotional- related representations in the brain are highly elaborate, and could thus be readily or even chronically activated. The differential sensitivity of the visual cortex, the prefrontal and parietal cortex to high arousing pictures implies distinct roles of visual and sensory regions in the registration and recollection of emotional experience in the brain in patients with PTSD. Overall, the data point to a network of a higher order sensory cortices in mediating the alert state in patients with PTSD.

Chapter 5

Synthesis and future directions

5.1 Some general considerations on human emotional stimulus processing

The bulk of research on human emotional stimulus processing has previously been observed by the application of an experimental paradigm. However, so far there is only preliminary evidence in relation to affective picture processing in PTSD. The present thesis addressed several hypotheses and experimental questions regarding psychophysiological changes, autonomic and somatic measures and subjective correlates of affective stimulus.

In study II we found that PTSD patients showed a differential sensitivity for the early time windows for high-arousing unpleasant pictures. Avoidance symptoms in PTSD patients were negatively correlated with the difference unpleasant minus neutral for the N1m time window suggesting that amplified responses for neutral pictures were negatively correlated with high avoidance scores. PTSD patients showed increased activity for high-arousing (pleasant and unpleasant) pictures for the late components suggesting cortical facilitation in attentional processes. Heart rate responses differed significantly among PTSD patients, schizophrenia inpatients and control subjects showing sustained heart rate acceleration for high-arousing unpleasant pictures in PTSD patients. In addition, increase in physiological reactivity including heart rate responses in PTSD patients suggests that these peripheral markers may be related with activation in higher order cortical networks. The effect of differential sensitivity for the visual N1m in PTSD patients for high-arousing unpleasant pictures was confirmed by the results of the source space projection in Study III showing that emotional modulation was evident at right occipital dipole sites but to a much lesser extent than in schizophrenia inpatients. Furthermore, study III revealed that, as evidenced by the MNE, high-arousing (unpleasant and pleasant) pictures elicited greater activity than low-arousing (neutral) pictures did in PTSD patients over frontal and frontoparietal cortical networks for the early P3m window, over anterior and posterior parietal regions for the late P3m window. Source space projection from subsequent time windows such as early and late P3m revealed specific enhancement of magneto-cortical activity in PTSD patients. This finding may reflect increased allocation of attentional resources to arousing stimuli over time in PTSD patients. In the last section the findings of the present investigation are summarized and special emphasis is given to their relevance for the initial hypothesis and experimental aims. The implications of these findings for the understanding of cortical networks involved in the emotional evaluation in PTSD patients are discussed on the basis of the models outlined above. Additionally, it is discussed whether these models provide a rational account for the assumption of current theories of emotion in PTSD.

5.1.1 MEG correlates during affective evaluation in PTSD patients at early stages of cortical processing. Evidence for a response sensitivity of the visual cortex in relation to emotional input in PTSD patients?

Elaboration of emotional stimuli in PTSD patients differed in several aspects from that of schizophrenia patients and healthy controls: First, the key finding in the second part of the present thesis concerns the earlier amplification for low-arousing (neutral) emotional pictures in PTSD patients such as found in the range of the N1m (140–220 ms) component. Further, evidence for this result comes from the highly significant negative correlation found between the total score of avoidance of PDS scale and the RMS difference value (unpleasant – neutral) for the N1m component. This result indicates that the amplified viewing of neutral pictures showed a significant inverse relationship with the total score of avoidance of PDS and therefore the amplified N1m for neutral pictures was predictive of high avoidance scores in torture victims and survivors of organized violence with PTSD. This finding, the amplification of neutral pictures in PTSD patients suggests impaired automatic allocation of processing resources to visual features that are motivationally significant. The data can be interpreted as follows: the specialization of visual cortices for aspects of early emotion discrimination and the involvement of the short-term conceptual memory system, in which stimuli reach meaningful representation, whereas long-term maintenance (consolidation) is transient.

One starting point for considering mechanisms underlying earlier stages of visual processing in PTSD might be recent theoretical approaches to emotional perception in humans. As was outlined in the introduction of this thesis (for further information, see Introduction), evidence accumulated so far emphasizes that the motivational/emotional relevance of a visual stimulus results in changes of sensory processing (P. J. Lang et al., 1990). In line with the idea that two motivational systems, one appetitive and one defensive, fundamentally organize emotion it has been suggested that these systems mediate interactions in the environment that either promote or threaten physical survival (Lane, Reiman et al., 1997). Accordingly, somatic, autonomic, and cortical events associated with orienting are automatically activated by emotional content of picture stimuli in a variety of paradigms (Cacioppo & Gardner, 1999). Furthermore, evidence from brain imaging research indicates, that this natural selective attention to emotional picture content is accompanied by widespread activation of the occipital cortex, suggesting that the visual system is particularly adjusted to detect and process motivationally relevant stimuli (Junghofer et al., 2001; P. J. Lang, Bradley, Fitzsimmons et al., 1998). In a recent fMRI study Lang and coworkers have addressed the question of whether the intensity of neuronal activity in the visual cortex is enhanced with increasing motivational significance of the visual stimulus (P. J. Lang, Bradley, Fitzsimmons et al., 1998). They found that viewing affective pictures (unpleasant or pleasant) resulted in more extensive functional activity in visual areas of the occipital cortex than viewing low-arousing neutral pictures. The authors suggested that reentrants afferents to visual cortices modulate processing of a given stimulus depending on its motivational significance. In addition to these early modulations by emotional intensity, several studies have reported ERP changes at earlier stages of visual processing. Junghöfer and coworkers (Junghofer et al., 2001) observed enhanced negativity at posterior recording sites in time ranges around 150 ms after picture onset for high-arousing slides compared to neutral ones. Furthermore, Keil and collaborators (Keil et al., 2001), using a hemifield design with affective pictures from the IAPS, reported differences in the N1 amplitude for high-arousing as compared with low-arousing stimuli. In another study Keil and coworkers (Keil et al., 2002) found that the visual N1 is modulated by affective arousal of visual stimuli. In addition, Keil and coworkers (Keil et al., 2003) using steady-state visual evoked brain potentials (ssVEPs) examined the allocation of processing resources to emotional picture stimuli. They found that viewing affective pictures (unpleasant or pleasant) as opposed to neutral pictures was associated with enhanced ssVEPs amplitude at parieto-occipital recording sites. The investigators suggested that findings are consistent with reentrant modulation of early visual processing by distributed networks including a variety of cortical and subcortical structures which are thought to depend on the motivational relevance (appetitive or defensive motivational engagement) of a given stimulus (Keil et al., 2003). In this sense, reentrant modulation of the visual cortex is thought to be a mechanism which enhances processing when a stimulus is motivationally relevant. On the other hand, selective attention research has suggested that a *sensory gain* mechanism might enhance sensory processing depending on the importance of the stimulus for the organism (Hillyard, Vogel, & Luck, 1998).

The idea that occipital cortical regions modulate emotional salient stimuli at an early stage of emotional processing indicates there must be a mechanism by which these regions receive reentrant projections from other structures. This finding corresponds to the evidence for rich connectivity between the amygdala complex and higher order visual cortex in mammals (Amaral, Price, Pitkanen, & Carmichael, 1992). The function of these projections on the visual stream has been suggested to be potentially neuromodulatory, perhaps in relation to an emotional state of the animal (Emery & Amaral, 2000). Thus, this natural selective attention may be an evolutionary adaptation promoting enhanced processing of potentially life-threatening or life-sustaining input (Everitt, Cardinal, Parkinson, & Robbins, 2003). Furthermore, Conturo and coworkers have found that fibers connecting the calcarine sulcus with the lateral nucleus of the amygdala using diffusion tensor MRI (DTI) in healthy humans. Furthermore, a growing body of work has used fMRI in healthy subjects demonstrating both an emotional effect in visual cortex (Bradley et al., 2003; Breiter et al., 1996; H. Critchley et al., 2000; Hendler, Rotshtein, & Hadar, 2001; Lane, Reiman et al., 1997; P. J. Lang, Bradley, Fitzsimmons et al., 1998; P. J. Lang, Fizsimmons, Bradley, Cuthbert, & Scott, 1996; Morris, Friston et al., 1998; Reiman et al., 1997; Taylor et al., 1998; Taylor et al., 2000) and an association between visual cortex and amygdala activation during emotional stimulation (Dolan & Morris, 2000; Rotshtein et al., 2001).

The discrepancy of findings regarding the emotional effect in the visual system, could be related to the fact that the emotional effect found in the visual system was confounded by non-emotional variables (meaningful objects and people vs noise) that could interact with the emotional valence of the visual stimuli. Other possibilities related to the discrepancy of the findings could be related to several differences between studies in relation to stimulation, such as modality (sounds, pictures, or script-driven imagery) and category of emotional stimuli (objects, people, or facial expressions).

Exposure to traumatic events can precipitate long-term changes in affect (Ettedgui & Bridges, 1985; M. J. Friedman, 1997; Yehuda, McFarlane, & Shalev, 1998) without any manifestation of structural brain damage (Markowitsch et al., 1998), but with long-term changes of synaptic plasticity (Garcia, 2001). In this sense, there are unanswered questions as to the extent of the effect of the emotional context on sensory processing in PTSD patients. The question is whether emotional inputs in PTSD patients undergo a different processing in early stages of emotional discrimination than non-affective stimuli do. Based on the idea that the occipital cortical regions modulate emotional inputs it seems that in the present thesis in the case of PTSD patients this modulation might be affected by the complexity of PTSD symptomatology. Taken together, the earlier amplification for neutral pictures in PTSD patients such as found in the range of the N1 component may indicate initial cortical inhibition of magnetic fields for visual features that are motivationally significant may be associated with PTSD symptoms.

Convergent evidence has come from studies of scalp-recorded ERPs where it has been demonstrated that PTSD patients show less activation in the visual cortex when they are asked to ignore trauma-related stimuli than when asked to ignore non-trauma related stimuli (Bleich et al., 1996). Furthermore, it has been assumed that traumatic experience leads to a pathological interaction between sensory processing and emotional context encoding (Newport & Nemeroff, 2000). This was lately supported by converging evidence based on sensory evoked potential findings according to which PTSD patients differed from controls in reactivity to deviant auditory stimuli at early stages of auditory processing (Gillette et al., 1997). PTSD patients exhibited significantly diminished habituation of the P1 potential. P1 potential habituation within the PTSD group correlated significantly with the intensity of PTSD re-experiencing symptoms, such as trauma-related nightmares and flashbacks. These findings are found to be consistent with a sensory gating defect at the brainstem level in PTSD patients and are further discussed in the context of other psychophysiological measures in PTSD patients. In addition, a recent study applying sensory evoked potentials found that PTSD subjects differed from controls in reactivity to deviant auditory stimuli. Moreover, this difference was detected at the early processing stages of the auditory pathway (Morgan & Grillon, 1999). Moreover, results from another study provide further support for sensory gating deficits in PTSD (Skinner et al., 1999). Results show that sensory gating of the P1 potential is significantly decreased at the 250 msec ISI, and that there is a numerical, but not statistically significant, decrease in sensory gating at the other intervals in both male and female PTSD subjects compared to all control groups. These investigators have interpreted these results as disturbances in sensory processing in PTSD in early stages of auditory processing. Since the P1 potential may be generated, at least in part, by the reticular activating system, dysregulation of sensory processing by elements of this system may be present in PTSD (Skinner et al., 1999). Moreover, other studies have demonstrated specific activation in the visual cortex in PTSD by using trauma-related stimuli, such as personal traumatic scripts (increased activation), (Rauch et al., 1996) or trauma related guided imagery (decreased activation) (Shin et al., 1999). Neylan and coworkers (Neylan et al., 1999) suggested that PTSD is associated with a general impairment of cognitive function that extends beyond the processing of trauma-specific stimuli. In their study they examined the P50 sensory gating to non-startle auditory stimuli in PTSD subjects and normal controls. PTSD subjects and normal controls did not differ with regard to the amplitude of the P50 response to the conditioning stimulus suggesting that PTSD is associated with impaired gating to non-startle trauma-neutral auditory stimuli.

Results from an fMRI study exploring sensory processing of trauma-related pictures in the visual cortex in PTSD found that the response to combat content evoked more activation in the visual cortex in PTSD subjects than in non-PTSD subjects when images were presented at below recognition threshold (Hendler et al., 2003). Although this study did not make a direct comparison between negative emotional stimuli related and unrelated to the traumatic experience, other studies found no evidence indicative of exaggerated activation in the visual cortex for masked negative facial expression (Rauch et al., 2000). The evidence provided in the present thesis underscores a considerable change in the response sensitivity of the visual cortex in relation to emotional input, especially for unpleasant high-arousing pictures. A greater response of the high order visual cortex is demonstrated in PTSD patients only for pleasant and neutral pictures showing no early discrimination between the two categories (Study II, Results, RMS, Study III, Results). Moreover, neutral input is amplified, whereas unpleasant arousing emotional input is attenuated at a very early stage in cortical afferent analysis. Although this finding may appear counterintuitive it is in fact compatible with the complexity of PTSD symptomatology. Symptoms of intrusive memories of the trauma coexist with avoidance of confrontation with trauma reminders (Foa et al., 1995). It seems that at early stages in cortical afferent analysis PTSD patients exhibit automatic mechanisms by which they avoid emotional unpleasant input. The hallmark symptoms of PTSD, including psychological numbing, may be related to a failure of the visual cortex to dampen the exaggerated symptoms of arousal and distress that are mediated through the amygdala in response to reminders of the traumatic event (Nutt & Malizia, 2004). One possible explanation might be based on the neural circuitry proposed by LeDoux (LeDoux, 1992, 1995): A direct thalamo-amygdala route can process crude sensory aspects of incoming stimuli and directly relay this information to the amygdala, allowing a rough categorization. Stimulus features that are consistent with threatening or aversive characteristics activate the amygdaloid nuclei, which in turn project to visual areas and thus provide a modulatory input that acts on the incoming sensory signal in a top-down manner.

Traumatic stressful life events might induce short-term sensory neuronal plasticity that is most probably mediated via its interconnections with subcortical structures involved in defensive and appetitive responding (Amaral et al., 1992; Everitt et al., 2003; LeDoux, 2000). It has been suggested that learning-related, cortical plasticity requires increased neuronal recruitment that could result in an increased activation in dedicated areas (Gauthier, Skudlarski, Gore, & Anderson, 2000). Specifically, it has been postulated that PTSD is maintained by learnt cortical and subcortical plastic changes (Wessa & Flor, 2002). Wessa and coworkers have assumed that classical conditioning may lead to an intense emotional memory of the trauma that is mainly implicit and related to plastic changes in subcortical structures such as the amygdala. Accumulated evidence from animal studies suggests that stress induces morphological and functional changes in the brain regions involved in emotional learning such as the hippocampus and the amygdala (Garcia, 2001; Kim & Diamond, 2002).

It remains an open question for prospective brain imaging studies to evaluate the effect of possible treatment approaches on cortical responses. This raises the question of whether changes will be observed for the pre-attentive visual processes or for later cortical processes (this will also be discussed later). Illnesses such as PTSD, which can be resistant to treatment in some patients, may perpetuate because of the perseveration of plasticity acquired by exposure of individuals to traumatic stress (M. J. Friedman, 1997; Tarrier, Sommerfield, Pilgrim, & Humphreys, 1999).

5.1.2 Are distributed cortical networks modulated by emotional arousal in subsequent time windows in PTSD?

The studies documented in this thesis -Study II and Study III- consistently showed pronounced effects of picture content in the early and late P3m time windows (350-700 ms) across groups (Study II, Results). As a result, these findings further support the view that the late positive wave behaves as a correlate of the emotional arousal-related modulation (P. J. Lang, Greenwald et al., 1993). Previous ERP studies have also noted differences in the magnitude of late positive going components as a function of emotional arousal (Cuthbert et al., 2000; Keil et al., 2002). In the case where distributed source modeling was conducted on data from dense electrode EEG arrays, grater dipole strength was found for these late ERP effects generated in visual areas of the occipital and temporal cortex as well as in the right hemispheric parietal areas (Keil et al., 2002).

In the present study, however, these effects were more pronounced in PTSD patients. They displayed greater magnetic responses to emotionally arousing (pleasant or unpleasant) pictures during time windows believed to reflect neurophysiological activity elicited by post-recognition processes. Furthermore, these effects as evidenced by the MNE elicited greater activity in PTSD patients over frontoparietal cortical networks (early P3m) and over parietal cortical networks (late P3m) (Study III, Results). One aim of the present thesis was to use the minimum norm estimation (MNE) procedure to complement the findings obtained by assessing the RMS data using the magnetoencephalogram (Chapter 3, Results). We found convergent results regarding the effects of emotional content for both the RMS data and the MNE dipole strength values. A number of points should be made to clarify the relevance of the present results with respect to the above question.

An important contribution to the understanding of specific enhancement for dipole strength in both P3m components for high-arousing pictures lies in the fact that the late positive wave as discussed already (Chapter 1, Introduction) has been interpreted as a measure of cortical activity for allocating more attentional resources to arousing stimuli over time. This basic function has important evolutionary relevance since it allows for optimal allocation of information processing resources. Furthermore, it has been suggested that this late positive wave, which is attenuated for less arousing neutral images (Ito, Larsen, Smith, & Cacioppo, 1998; Keil et al., 2002; Palomba et al., 1997; Schupp et al., 2000) can be maintained for several seconds until picture presentation offset and has been characterized as reflecting greater activity in systems processing different aspects of the stimulus, including their motivational relevance (Cuthbert et al., 2000).

An ERP that has been studied extensively in PTSD patients and has been shown to be associated with cognitive recognition of the significance of particular stimuli is the P3 component. Research has shown that the P3 probably reflects a group of potentials that are related to different types of attentional processes. Attias and coworkers (Attias, Bleich, Furman et al., 1996) have reported significantly augmented P3a amplitude at all midline electrodes for combat relevant stimuli with the largest increase to be found at the frontal site (Fz). While P3b was also found to be generally augmented it was maximal at posterior locations. It seems that P3a occurs, regardless of task relevance, in response to particularly salient stimuli and is distributed at more anterior electrode sites. In another study, Stanford and coworkers (Stanford et al., 2001) suggested that among PTSD-diagnosed veterans, greater attentional resources and concurrent neurophyiological activity were allocated to trauma-relevant stimuli across both oddball tasks while fewer resources were available for the processing of trauma-irrelevant information. The investigators interpreted these findings along resource allocation models of PTSD.

In the present thesis, magnetocortical responses to affectively arousing (unpleasant or pleasant) pictures that differentiated groups by dipole strength showed a consistent evolution in time among groups, as compared with neutral stimuli (Study III, Results). As illustrated in the statistical parametric maps of estimated dipole strength, content effects among groups suggested differential activation of cortical structures (Study III, Results). Arousal related modulations were observed in PTSD patients for the early P3m window over prefrontal and frontoparietal regions with a left hemispheric dominance. The source areas of these effects with the greatest activity were located over frontoparietal dipole sites for left hemisphere. Schizophrenia inpatients exhibited enhanced dipole strength over higher order visual cortical areas with a left hemispheric dominance. Control subjects showed enhanced dipole strength over fronto-parietal dipole sites for left hemisphere and over temporo-parietal dipole sites for the right hemisphere but to a lesser extent than PTSD patients (Study III, Results).

However, activity within these cortical regions has been reported for a variety of affect-related tasks, including symptom provocation in patients suffering from anxiety disorders (Rauch et al., 1996; Rauch et al., 2000), as well as emotional processing in healthy volunteers (Lane et al., 1999; Whalen, Bush et al., 1998). This suggests that the circuitry recruited to process affective pictures for subsequent time windows in PTSD patients was restricted to prefrontal and frontoparietal dipole locations. It seems that in PTSD patients affective modulation is processed differently than in schizophrenia inpatients and control subjects at the sensory level (Hendler et al., 2003). Several studies have implicated frontal cortical areas modulating emotional responsiveness in PTSD patients (Vermetten & Bremner, 2002). Thus, the absence of activation in prefrontal regions in schizophrenia inpatients is consistent with the conclusion that the activation of these cortical areas in PTSD patients could be a specific response. In line with the idea of sensory modulation by the brain's motivational system, recent results of functional neuroimaging studies of the prefrontal cortex during the viewing of trauma related scenes or pictures in PTSD patients showed increases in the prefrontal cortex (Matsuo et al., 2003; Zubieta et al., 1999). This ties in with the role of these cortical substrates in PTSD patients being involved in the modulation of arousal (Zubieta et al., 1999). Recent advances in studies using metabolic and blood flow techniques have also provided insights into central nervous correlates of affective picture processing suggesting differential functional activation at frontoparietal dipole sites for picture stimuli judged to be high in emotional arousal compared with less affectively engaging pictures and thus involving specific cortical networks implicated in attention (Corbetta, 1998; Le et al., 1998; Rushworth et al., 2001) and orienting and maintaining the alert state (Fernandez-Duque & Posner, 2001).

Convergent evidence points to reciprocal connections between the amygdala and the ventral/medial prefrontal cortex. Rauch and colleagues proposed a model of PTSD emphasizing the amygdala and its interaction with limbic and paralimbic structures. According to this model amygdala hyper-responsivity to threat-related stimuli is perhaps exacerbated by ventral/medial prefrontal cortex and hippocampus due to inefficacy of top-down modulation. These findings support an evolving speculative model of PTSD focusing on the interplay between these frontal cortical regions, the amygdala and the hippocampus.

Mapping of statistical parameters indicated that the modulation of dipole strength as a function of emotional arousal for the late P3m time window showed specific enhancement for emotional content in PTSD patients over frontal dipole sites and posterior parietal dipole sites with a left hemispheric preponderance. Such a modulation, but to a much lesser extent, was also evident at temporal dipole sites with a right hemispheric predominance. An enhancement of dipole strength in the late P3m time window was found for high-arousing pictures in schizophrenia inpatients over right parietal and temporal dipole sites. Furthermore, a modulation by emotional arousal was observed in schizophrenia inpatients over left parietal dipole sites but to a lesser extent. A modulation for affective picture processing was observed in control subjects occurring in bilateral anterior sites associated with temporal cortex with greatest activity over left hemisphere areas. This finding is in line with studies that have implicated cerebral networks in healthy people that modulate emotion processing such as temporal and parts of the parietal cortex (Adolphs et al., 1996; LeDoux, 1995).

Anatomical studies have reported that the posterior parietal cortex is one major source of top-down control of ventral stream areas (Hopfinger et al., 2000; Kastner et al., 1999; Kastner & Ungerleider, 2001). Furthermore, neuroimaging studies in humans have shown activation of posterior parietal cortex in many tasks that require top-down attentional control. It is suggested that the parietal cortex and prefrontal cortex are involved in visuo-spatial processing that is an important component in patients with PTSD. It is suggested that connections between the parietal and prefrontal cortex are required in order to permit the organism to rapidly and efficiently execute motor responses to threat (Vermetten & Bremner, 2002). Most interestingly, in our study only PTSD patients presented this network pattern for the late P3m time window which could be interpreted as more characteristic of PTSD. In the current study, this would suggest that the increased reactivity seen in PTSD patients in the late P3m time window might reflect an involvement of regions that are activated both by pleasant and unpleasant pictures and thus may be involved in the arousal component of emotional response. In general, these findings point to a network of related regions, which are mobilized in patients with PTSD during emotional stimulus processing.

5.1.3 Emotional modulation of the eye-blink and visceral responses to an acoustic startle probe. Specific autonomic (e.g., heart rate change) and somatic reflexes (e.g., startle change) in the fear-network of PTSD patients?

One possible approach to answer this questions lies in the motivational systems (appetitive and defensive) which mediate specific autonomic (e.g., heart rate change) and somatic reflexes (e.g., startle change) and are thought to reflect an evolutionary adaptation to potentially life-threatening or life-sustaining input (P. J. Lang et al., 2000). In the present thesis this is supported by both measures of the heart rate and startle changes. Consistent with the motivational hypothesis, cardiac changes in response to environmental demands reflect attentional and perceptual mechanisms aimed at facilitating or inhibiting the processing of relevant sensory inputs. This sequential defense reaction is also supported by recent neurophysiological studies on fear and anxiety (Davis, 1996; Kapp, Whalen, & Supple, 1992; LeDoux, 2000). According to the LeDoux (LeDoux, Cicchetti et al., 1990) model (for further Information see Introduction) this defense reaction implicates a neural circuit which is initiated when relevant sensory input activates the basolateral nuclei of the amygdala. More recent research has demonstrated the role that the bed nucleus of stria terminalis plays in anxiety (Bradley et al., 2003). Moreover, both structures receive sensory information from the basolateral nucleus of the amygdala and project it to various hypothalamic sites, the central gray, and brainstem target areas that directly mediate the specific responses characterizing fear and anxiety, e.g., freezing, and hypervigilance, autonomic and somatic reactions. In this context, emerging evidence indicates that aversive pictures usually generate a sustained heart rate deceleration with a less clear triphasic pattern as compared to neutral and pleasant pictures. Pleasant pictures usually provoke a greater initial deceleration and a more pronounced accelerative component than neutral pictures (Bradley et al., 2001).

Analysis of cardiac responses in the present thesis yielded several important results. The classic triphasic waveform (Gatchel & Lang, 1973), consisting of an initial deceleration, subsequent acceleration, and a secondary deceleration time was only obtained in schizophrenia inpatients and healthy controls. PTSD patients exhibited the most pronounced cardiac acceleration to high-arousing unpleasant pictures as compared to schizophrenia inpatients and to control subjects over the whole picture presentation time. In line with other studies heart rate changes in schizophrenic subjects and in controls did not differ significantly (Schlenker et al., 1995; Volz et al., 2003) with regard to affective valence, although autonomic activity of schizophrenic patients was generally reduced compared to healthy control subjects. Attenuation of visceral reactivity in schizophrenic patients may account for a decreased stimulus-related modulation. The elevated heart rate responses to unpleasant stimuli in PTSD patients are consistent with other studies that showed that heart rate increased in trauma victims in response to pictorial representations (Buckley & Kaloupek, 2001). Contemporary research on PTSD has demonstrated increased heart rate responses during symptom provocation paradigms (Shalev et al., 1992). Furthermore, Blanchard et al. (E. B. Blanchard et al., 1991) also observed elevations in basal cardiovascular activity, particularly heart rate, in PTSD patients as compared to healthy volunteers. Similarly, Hohn-Saric and McLeod (Hoehn-Saric & McLeod, 1993) have concluded that PTSD patients show an exaggerated autonomic reactivity to stimuli or contexts reminiscent of precipitating traumatic events. In addition to this, convergent evidence suggests a slower rate of habituation of autonomic responses over trials in anxiety patients (Berntson et al., 1998). Furthermore, PTSD patients may display a pattern of autonomic response roughly paralleling their pattern of behavioral /affective reactivity (Hoehn-Saric & McLeod, 1993). On the basis of evidence that heart rate measures become integrated with ongoing behavior and information processing, emerging evidence suggests that the enhanced reactivity seen in PTSD patients might be characteristic of this disorder (Gerardi, Keane, Cahoon, & Klauminzer, 1994; McFall, Murburg, Ko, & Veith, 1990; Shalev et al., 1992, 1993). Evidence is accruing through various studies that avoidance, one of the cardinal features in PTSD, is associated also with cardioacceleratory responses to non-signal auditory stimuli (Orr, Lasko, Shalev, & Pitman, 1995; Shalev et al., 1992). However, in the present thesis the significant positive correlation we found between the total PDS-avoidance score and the heart rate responses for the difference unpleasant minus neutral suggests this difference can be attributed to the high-arousing unpleasant stimuli. Drawing on the support of magnetocortical data, it seems that in cortical systems at early stages of processing the resources available for processing emotional pictures in PTSD patients are inhibited whereas processing in the autonomic system is accompanied by pronounced effects of cardiac acceleration in response to arousing unpleasant stimuli. One might speculate that PTSD represents a state of central nervous system (CNS) sensitivity and that PTSD patients, when faced with emotional stimuli, enter a state of protective inhibition (Paige et al., 1990) while the 'periphery' remains intact. In addition, the present findings show that patterns of both increased and decreased activation in cortical brain systems are related to ongoing changes in cardiac autonomic activity (Gianaros et al., 2004). The finding that late P3m responses for the difference pleasant minus neutral correlated with increased heart rate responses supports this notion. Those PTSD patients who exhibited higher cortical positivity to neutral pictures also showed higher heart rate acceleration. For the early components we did not find any significant correlations between MEG and HR responses. It is also reasonable that the late P3m component was associated with HR changes to a greater extent than early components, due to different response latencies between the two systems (Palomba et al., 1997).

Regarding somatic reflexes the data of the present thesis add to the growing body of evidence supporting the existence of an exaggerated startle response in PTSD patients. The positive correlation we found between startle response for the difference unpleasant minus neutral and the total HSCL-Anxiety score suggests that startle and anxiety are core clinical features of the human psychological response to traumatic experiences (Grillon, Morgan, Southwick, Davis, & Charney, 1996; Morgan et al., 1997; Morgan et al., 1995; Orr et al., 1995). Moreover, it seems that exaggerated startle potentiation in PTSD patients resulted from highly arousing unpleasant stimuli (Bradley et al., 1990). We may speculate that the exaggerated startle response seen in PTSD patients is part of a conditioned response to stressful situations or stimuli reminiscent of trauma (Hitchcock et al., 1989). It should be emphasized that in the present study, in the first block of picture presentation, although the startle reflex in PTSD patients was significantly greater than in schizophrenia patients and control subjects, we did not find a significant interaction between affective valence and group. In the second block, however, the overall eye-blink magnitude was significantly greater in PTSD patients than in schizophrenia patients and a significant interaction was observed between affective category and group.

Furthermore, evidence from animal data clearly links potentiated startle to the same neural structures involved in the general mediation of fear/defense responses. The neural pathway underlying fear-potentiated startle in rats suggests an important modulatory role for the amygdala and its projections. Furthermore, lesions of the central nucleus or the lateral and basolateral nuclei of the amygdala inhibit the expression of fear-potentiated startle, whereas electrical stimulation of the central nucleus increases startle amplitude (Davis, Falls, Campeau, & Kim, 1993; Davis, Walker, & Lee, 1999). Moreover, the same structures and connections exist in the human brain, and appear to have parallel functions. In humans lesions of the amygdala resulted in failure to exhibit the typical startle potentation induced by unpleasant or frightening stimuli (Angrilli et al., 1996; Funayama, Grillon, Davis, & Phelps, 2001). Further evidence for the crucial role of the amygdaloid complex on startle reactions in humans comes from a PET study where Pissiota and coworkers studied neural networks associated with startle modulation in a group of subjects with specific snake phobia. They pointed to the involvement of the ACC in the processing of startle stimuli during emotionally aversive experiences (Pissiota et al., 2003).

Furthermore, it is conceivable that PTSD patients suffer from a dysregulation of hippocampal activity that leads to an abnormal processing of contextual information (Morgan et al., 1995). Such a hypothesis could account for the increased anxiety response and the increased startle response displayed by PTSD patients in the more aversive experimental environment of the MEG chamber. It is also possible that the novelty of the environment was responsible for the exaggerated startle responses seen in PTSD patients. Lang and colleagues have recently reported that general startle sensitivity may characterize individuals with negative affect. They further speculated that these individuals might be particularly vigilant and apprehensive when confronted with novel or unusual situations (P. J. Lang et al., 2000). The exaggerated startle response seen PTSD patients might be due to a combination of an abnormal processing of contextual information and a novel environment.

5.2 An integrated account of a speculative model of human emotional stimulus processing in PTSD

Considered as a whole, the evidence provided so far in the present thesis suggests that the processing of emotional visual stimuli in PTSD recruits a number of visual areas of the occipital cortex at early stages of sensory processing whereas limbic areas, such as the amygdala, and non-limbic areas, including ventral and medial prefrontal cortices as well as frontoparietal cortices are involved at later stages in cortical afferent analysis. These findings may especially shed some light on the interplay between visual cortex and limbic regions and between prefrontal and parietal cortex and limbic regions in processing emotional valence of stimuli. In the following paragraph a speculative scheme might visualize some structures, such as occipital cortical areas, the amygdala and regions of the prefrontal and frontoparietal cortices.

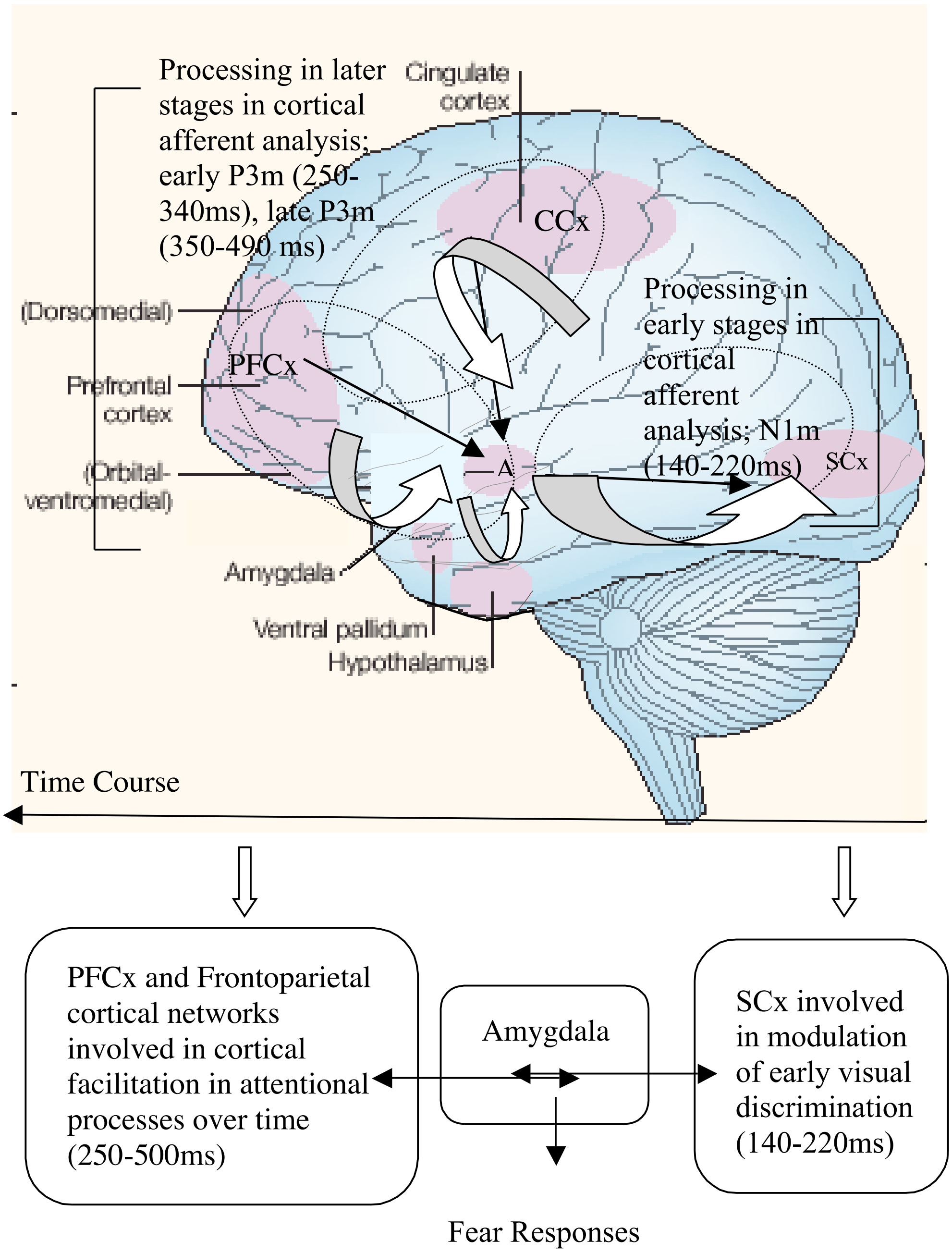

Figure 5.1: Graphical illustration of a speculative model of human emotional stimulus processing in PTSD as a function of time as outlined in the Conclusion section of this thesis. Anatomical image adapted from Appleton and Lange (Martin, 1996) (a) Key structures within a generalized emotional brain; the figure does not show the relative depths of the various structures, merely their two-dimensional location within the brain schematic. As this is a lateral view, only one member of bilateral pairs of structures can be seen: A, amygdala; CCx, Cingulate cortex; PFCx, Prefrontal cortex; Scx, Striate cortex (b) Connections.

Evidence from the present thesis suggests that regions of the occipital cortex play a critical role in perceptual processing of emotionally relevant visual stimuli. To understand the neural mechanisms of emotional stimulus processing it is important to have in mind the following model as proposed by LeDoux. The amygdala participates in the recognition of emotional signals via at least two classes of input mechanisms: a subcortical route via the superior colliculus and the pulvinar thalamus and a cortical route via the visual neocortex (LeDoux, 1992, 1995). Subliminally presented facial expressions of fear activate the amygdala in normal subjects (Whalen, Rauch et al., 1998) and give an exaggerated amygdala response in PTSD patients (Rauch et al., 2000). Electrophysiological responses in the human amygdala are first seen at ~120ms (Halgren et al., 1994) and probably show differential effects as a function of emotion category at ~150ms (Ioannides, 2001). During a higher level of visual processing affective evaluation is assumed to recruit coordinated activity of high-level visual cortex, amygdala and areas in the prefrontal and frontoparietal cortex. This process can be monitored using event-related magnetic field (ERFs) components such as the early P3m (250-340ms) and the lateP3m (350-500ms). In the present thesis using MEG and a source estimation technique high-arousing pictures elicited greater activity in PTSD patients over prefrontal and frontoparietal cortical networks. In the present context, the late affects are best explained as manifestations of network activity as proposed by Lang (P. J. Lang, 1994). Thus, they would reflect emotional arousal in cortical areas that have been activated via ‘motivated attention’ mechanisms (P. J. Lang, 1994).

5.3 Conclusions and future directions

Taken together, the present thesis points to the following conclusions. First, stressful life events are long-term stored in the brain architecture as fear networks (Elbert, 2005; (P. J. Lang et al., 2000). Furthermore, trauma-related representations in the brain are highly elaborate and can readily be reactivated (Hendler et al., 2001; Hendler et al., 2003; P. J. Lang et al., 2000). Second, early modulations associated with emotional stimulus processing in PTSD are affected by the complexity of PTSD symptomatology; the earlier amplification for neutral pictures seen in PTSD patients such as found in the range of the N1m component suggests initial cortical inhibition of magnetic fields for visual features that are motivationally significant and may therefore be associated with PTSD symptoms. The findings point toward possible plasticity mechanisms in the high order visual cortex that can be attributed to PTSD symptomatology. Third, the circuitry recruited to process affective pictures for later time windows in PTSD patients is restricted to prefrontal and frontoparietal dipole locations thereby reflecting the role of cortical facilitation in attentional processes for motivationally relevant stimuli.

Further work is needed to reveal these mechanisms of the fear-network in PTSD patients in more detail, specifying how magnetocortical responses at early and later stages of stimulus processing might change during interventions such as testimony therapy (Schauer, Neuner, & Elbert, 2005). This endeavor will require the use of analogous experimental designs (emotional stimuli from the IAPS) and comparable methods such as magnetic source imaging and distributed source modeling. The results of the present thesis raise the question of whether effects for early perceptual visual processes, later cortical processes or both will be dissipated after treatment.

Bibliography

Adamec, R. E., & Shallow, T. (1993). Lasting effects on rodent anxiety of a single exposure to a cat. *Physiol Behav, 54*(1), 101-109.
Addington, D., Addington, J., & Maticka-Tyndale, E. (1993). Assessing depression in schizophrenia: the Calgary Depression Scale. *Br J Psychiatry Suppl*(22), 39-44.
Adler, C., & Hillhouse, J. (1996). Stress, health, and immunity: a review of the literature. In T. W. Miller (Ed.), *Theory and Asessment of Stressful Life Events* (pp. 109-138). Madison, Conn: International Universities Press.
Adolphs, R. (2002). Neural systems for recognizing emotion. *Curr Opin Neurobiol, 12*(2), 169-177.
Adolphs, R. (2003). Cognitive neuroscience of human social behaviour. *Nat Rev Neurosci, 4*(3), 165-178.
Adolphs, R., Damasio, H., Tranel, D., & Damasio, A. R. (1996). Cortical systems for the recognition of emotion in facial expressions. *J Neurosci, 16*(23), 7678-7687.
Adolphs, R., Tranel, D., Damasio, H., & Damasio, A. (1994). Impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala. *Nature, 372*(6507), 669-672.
Adolphs, R., Tranel, D., Damasio, H., & Damasio, A. R. (1995). Fear and the human amygdala. *J Neurosci, 15*(9), 5879-5891.
Aggleton, J. P. (1993). The contribution of the amygdala to normal and abnormal emotional states. *Trends Neurosci, 16*(8), 328-333.
Amaral, D. G., Price, J. L., Pitkanen, A., & Carmichael, S. T. (1992). Anatomical organization of the primate amygdaloid complex. In J. P. Aggleton (Ed.), *The amygdala: Neurobiological aspects of emotion, memory, and mental dysfuntion* (pp. 1-66). New York: Wiley-Liss.
Anderson, S. W., Bechara, A., Damasio, H., Tranel, D., & Damasio, A. R. (1999). Impairment of social and moral behavior related to early damage in human prefrontal cortex. *Nat Neurosci, 2*(11), 1032-1037.
Andreasen, N. C. (1982). Negative symptoms in schizophrenia. Definition and reliability. *Arch Gen Psychiatry, 39*(7), 784-788.
Angrilli, A., Mauri, A., Palomba, D., Flor, H., Birbaumer, N., Sartori, G., et al. (1996). Startle reflex and emotion modulation impairment after a right amygdala lesion. *Brain, 119 (Pt 6)*, 1991-2000.
Armony, J. L., & LeDoux, J. E. (1997). How the brain processes emotional information. *Ann N Y Acad Sci, 821*, 259-270.
Arndt, S., Cizadlo, T., Andreasen, N. C., Heckel, D., Gold, S., & O'Leary, D. S. (1996). Tests for comparing images based on randomization and permutation methods. *J Cereb Blood Flow Metab, 16*(6), 1271-1279.
Attias, J., Bleich, A., Furman, V., & Zinger, Y. (1996). Event-related potentials in post-traumatic stress disorder of combat origin. *Biol Psychiatry, 40*(5), 373-381.
Attias, J., Bleich, A., & Gilat, S. (1996). Classification of veterans with post-traumatic stress disorder using visual brain evoked P3s to traumatic stimuli. *Br J Psychiatry, 168*(1), 110-115.
Augustine, J. R. (1985). The insular lobe in primates including humans. *Neurol Res, 7*(1), 2-10.
Back, S., Dansky, B. S., Coffey, S. F., Saladin, M. E., Sonne, S., & Brady, K. T. (2000). Cocaine dependence with and without post-traumatic stress disorder: a comparison of substance use, trauma history and psychiatric comorbidity. *Am J Addict, 9*(1), 51-62.

Baillet, S., Riera, J. J., Marin, G., Mangin, J. F., Aubert, J., & Garnero, L. (2001). Evaluation of inverse methods and head models for EEG source localization using a human skull phantom. *Phys Med Biol, 46*(1), 77-96.

Balaban, M. T., & Taussig, H. N. (1994). Salience of fear/threat in the affective modulation of the human startle blink. *Biol Psychol, 38*(2-3), 117-131.

Basoglu, M., Paker, M., Paker, O., Ozmen, E., Marks, I., Incesu, C., et al. (1994). Psychological effects of torture: a comparison of tortured with nontortured political activists in Turkey. *Am J Psychiatry, 151*(1), 76-81.

Bauer, R. M. (1998). Physiologic measures of emotion. *J Clin Neurophysiol, 15*(5), 388-396.

Bechara, A., Damasio, A. R., Damasio, H., & Anderson, S. W. (1994). Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition, 50*(1-3), 7-15.

Bechara, A., Damasio, H., Tranel, D., & Damasio, A. R. (1997). Deciding advantageously before knowing the advantageous strategy. *Science, 275*(5304), 1293-1295.

Bechara, A., Tranel, D., & Damasio, H. (2000). Characterization of the decision-making deficit of patients with ventromedial prefrontal cortex lesions. *Brain, 123 (Pt 11)*, 2189-2202.

Bechara, A., Tranel, D., Damasio, H., Adolphs, R., Rockland, C., & Damasio, A. R. (1995). Double dissociation of conditioning and declarative knowledge relative to the amygdala and hippocampus in humans. *Science, 269*(5227), 1115-1118.

Bechara, A., Tranel, D., Damasio, H., & Damasio, A. R. (1996). Failure to respond autonomically to anticipated future outcomes following damage to prefrontal cortex. *Cereb Cortex, 6*(2), 215-225.

Beck, A. T. (1976). *Cognitive therapy and the emotional disorders*. New York: International Press.

Beck, J. C., & van der Kolk, B. (1987). Reports of childhood incest and current behavior of chronically hospitalized psychotic women. *Am J Psychiatry, 144*(11), 1474-1476.

Bernet, C. Z., & Stein, M. B. (1999). Relationship of childhood maltreatment to the onset and course of major depression in adulthood. *Depress Anxiety, 9*(4), 169-174.

Berntson, G. G., Sarter, M., & Cacioppo, J. T. (1998). Anxiety and cardiovascular reactivity: the basal forebrain cholinergic link. *Behav Brain Res, 94*(2), 225-248.

Berntson, G. G., Sarter, M., & Cacioppo, J. T. (2003). Ascending visceral regulation of cortical affective information processing. *Eur J Neurosci, 18*(8), 2103-2109.

Bierer, L. M., Yehuda, R., Schmeidler, J., Mitropoulou, V., New, A. S., Silverman, J. M., et al. (2003). Abuse and neglect in childhood: relationship to personality disorder diagnoses. *CNS Spectr, 8*(10), 737-754.

Binder, R. L., McNiel, D. E., & Goldstone, R. L. (1996). Is adaptive coping possible for adult survivors of childhood sexual abuse? *Psychiatr Serv, 47*(2), 186-188.

Blanchard, D. C., & Blanchard, R. J. (1972). Innate and conditioned reactions to threat in rats with amygdaloid lesions. *J Comp Physiol Psychol, 81*(2), 281-290.

Blanchard, E. B., Kolb, L. C., & Prins, A. (1991). Psychophysiological responses in the diagnosis of posttraumatic stress disorder in Vietnam veterans. *J Nerv Ment Dis, 179*(2), 97-101.

Bleich, A. V., Attias, J., & Furman, V. (1996). Effect of repeated visual traumatic stimuli on the event related P3 brain potential in post-traumatic stress disorder. *Int J Neurosci, 85*(1-2), 45-55.

Bleuler, E. (1950). *Dementia praecox or the group of schizophrenias* (J. Zinkin, Trans.). New York: International Universities Press.

Blomhoff, S., Reinvang, I., & Malt, U. F. (1998). Event-related potentials to stimuli with emotional impact in posttraumatic stress patients. *Biol Psychiatry, 44*(10), 1045-1053.

Board, F., Persky, H., & Hamburg, D. A. (1956). Psychological stress and endocrine functions; blood levels of adrenocortical and thyroid hormones in acutely disturbed patients. *Psychosom Med, 18*(4), 324-333.

Bordi, F., & LeDoux, J. (1992). Sensory tuning beyond the sensory system: an initial analysis of auditory response properties of neurons in the lateral amygdaloid nucleus and overlying areas of the striatum. *J Neurosci, 12*(7), 2493-2503.

Bradley, M. M., Codispoti, M., Cuthbert, B. N., & Lang, P. J. (2001). Emotion and motivation I: defensive and appetitive reactions in picture processing. *Emotion, 1*(3), 276-298.

Bradley, M. M., Cuthbert, B. N., & Lang, P. J. (1990). Startle reflex modification: emotion or attention? *Psychophysiology, 27*(5), 513-522.

Bradley, M. M., Cuthbert, B. N., & Lang, P. J. (1996). Picture media and emotion: effects of a sustained affective context. *Psychophysiology, 33*(6), 662-670.

Bradley, M. M., & Lang, P. J. (1994). Measuring emotion: the Self-Assessment Manikin and the Semantic Differential. *J Behav Ther Exp Psychiatry, 25*(1), 49-59.

Bradley, M. M., & Lang, P. J. (2000). Affective reactions to acoustic stimuli. *Psychophysiology, 37*(2), 204-215.

Bradley, M. M., Sabatinelli, D., Lang, P. J., Fitzsimmons, J. R., King, W., & Desai, P. (2003). Activation of the visual cortex in motivated attention. *Behav Neurosci, 117*(2), 369-380.

Brammer, M. J., Bullmore, E. T., Simmons, A., Williams, S. C., Grasby, P. M., Howard, R. J., et al. (1997). Generic brain activation mapping in functional magnetic resonance imaging: a nonparametric approach. *Magn Reson Imaging, 15*(7), 763-770.

Breiter, H. C., Etcoff, N. L., Whalen, P. J., Kennedy, W. A., Rauch, S. L., Buckner, R. L., et al. (1996). Response and habituation of the human amygdala during visual processing of facial expression. *Neuron, 17*(5), 875-887.

Bremner, J. D. (1999a). Alterations in brain structure and function associated with post-traumatic stress disorder. *Semin Clin Neuropsychiatry, 4*(4), 249-255.

Bremner, J. D. (1999b). Does stress damage the brain? *Biol Psychiatry, 45*(7), 797-805.

Bremner, J. D., Krystal, J. H., Southwick, S. M., & Charney, D. S. (1995). Functional neuroanatomical correlates of the effects of stress on memory. *J Trauma Stress, 8*(4), 527-553.

Bremner, J. D., Narayan, M., Staib, L. H., Southwick, S. M., McGlashan, T., & Charney, D. S. (1999). Neural correlates of memories of childhood sexual abuse in women with and without posttraumatic stress disorder. *Am J Psychiatry, 156*(11), 1787-1795.

Bremner, J. D., Staib, L. H., Kaloupek, D., Southwick, S. M., Soufer, R., & Charney, D. S. (1999). Neural correlates of exposure to traumatic pictures and sound in Vietnam combat veterans with and without posttraumatic stress disorder: a positron emission tomography study. *Biol Psychiatry, 45*(7), 806-816.

Breslau, N., Davis, G. C., Andreski, P., & Peterson, E. (1991). Traumatic events and posttraumatic stress disorder in an urban population of young adults. *Arch Gen Psychiatry, 48*(3), 216-222.

Brewin, C. R., Rose, S., Andrews, B., Green, J., Tata, P., McEvedy, C., et al. (2002). Brief screening instrument for post-traumatic stress disorder. *Br J Psychiatry, 181*, 158-162.

Briere, J., Woo, R., McRae, B., Foltz, J., & Sitzman, R. (1997). Lifetime victimization history, demographics, and clinical status in female psychiatric emergency room patients. *J Nerv Ment Dis, 185*(2), 95-101.

Briere, J., & Zaidi, L. Y. (1989). Sexual abuse histories and sequelae in female psychiatric emergency room patients. *Am J Psychiatry, 146*(12), 1602-1606.

Brown, G. R., & Anderson, B. (1991). Psychiatric morbidity in adult inpatients with childhood histories of sexual and physical abuse. *Am J Psychiatry, 148*(1), 55-61.

Bryant, R. A., & Harvey, A. G. (1997). Attentional bias in posttraumatic stress disorder. *J Trauma Stress, 10*(4), 635-644.
Bryer, J. B., Nelson, B. A., Miller, J. B., & Krol, P. A. (1987). Childhood sexual and physical abuse as factors in adult psychiatric illness. *Am J Psychiatry, 144*(11), 1426-1430.
Buckley, T. C., & Kaloupek, D. G. (2001). A meta-analytic examination of basal cardiovascular activity in posttraumatic stress disorder. *Psychosom Med, 63*(4), 585-594.
Bush, G., Luu, P., & Posner, M. I. (2000). Cognitive and emotional influences in anterior cingulate cortex. *Trends Cogn Sci, 4*(6), 215-222.
Cacioppo, J. T., & Gardner, W. L. (1999). Emotion. *Annu Rev Psychol, 50*, 191-214.
Campo, A. T., & Rohner, R. P. (1992). Relationships between perceived parental acceptance-rejection, psychological adjustment, and substance abuse among young adults. *Child Abuse Negl, 16*(3), 429-440.
Canon, W. B. (1915). *Bodily changes in pain, hunger, fear, and rage*. New York: D. Aplleton & Co.
Carmen, E. H., Rieker, P. P., & Mills, T. (1984). Victims of violence and psychiatric illness. *Am J Psychiatry, 141*(3), 378-383.
Carpenter, W. T., Jr., Heinrichs, D. W., & Wagman, A. M. (1988). Deficit and nondeficit forms of schizophrenia: the concept. *Am J Psychiatry, 145*(5), 578-583.
Carretie, L., Iglesias, J., & Garcia, T. (1997). A study on the emotional-processing of visual stimuli through event-related potentials. *Brain Cogn, 34*(2), 207-217.
Cascardi, M., Mueser, K. T., DeGiralomo, J., & Murrin, M. (1996). Physical aggression against psychiatric inpatients by family members and partners. *Psychiatr Serv, 47*(5), 531-533.
Charles, G., Hansenne, M., Ansseau, M., Pitchot, W., Machowski, R., Schittecatte, M., et al. (1995). P300 in posttraumatic stress disorder. *Neuropsychobiology, 32*(2), 72-74.
Charney, D. S. (2004). Psychobiological mechanisms of resilience and vulnerability: implications for successful adaptation to extreme stress. *Am J Psychiatry, 161*(2), 195-216.
Chu, J. A., & Dill, D. L. (1990). Dissociative symptoms in relation to childhood physical and sexual abuse. *Am J Psychiatry, 147*(7), 887-892.
Chu, J. A., & Dill, D. L. (1991). Dissociation, borderline personality disorder, and childhood trauma. *Am J Psychiatry, 148*(6), 812-813.
Codispoti, M., Bradley, M. M., & Lang, P. J. (2001). Affective reactions to briefly presented pictures. *Psychophysiology, 38*(3), 474-478.
Cohen, P., Brown, J., & Smaile, E. (2001). Child abuse and neglect and the development of mental disorders in the general population. *Dev Psychopathol, 13*(4), 981-999.
Corbetta, M. (1998). Frontoparietal cortical networks for directing attention and the eye to visual locations: identical, independent, or overlapping neural systems? *Proc Natl Acad Sci U S A, 95*(3), 831-838.
Coverdale, J. H., & Turbott, S. H. (2000). Sexual and physical abuse of chronically ill psychiatric outpatients compared with a matched sample of medical outpatients. *J Nerv Ment Dis, 188*(7), 440-445.
Coyne, J. C., & Whiffen, V. E. (1995). Issues in personality as diathesis for depression: the case of sociotropy-dependency and autonomy-self-criticism. *Psychol Bull, 118*(3), 358-378.
Craine, L. S., Henson, C. E., Colliver, J. A., & MacLean, D. G. (1988). Prevalence of a history of sexual abuse among female psychiatric patients in a state hospital system. *Hosp Community Psychiatry, 39*(3), 300-304.

Crespo-Facorro, B., Paradiso, S., Andreasen, N. C., O'Leary, D. S., Watkins, G. L., Ponto, L. L., et al. (2001). Neural mechanisms of anhedonia in schizophrenia: a PET study of response to unpleasant and pleasant odors. *Jama, 286*(4), 427-435.

Critchley, H., Daly, E., Phillips, M., Brammer, M., Bullmore, E., Williams, S., et al. (2000). Explicit and implicit neural mechanisms for processing of social information from facial expressions: a functional magnetic resonance imaging study. *Hum Brain Mapp, 9*(2), 93-105.

Critchley, H. D., Daly, E. M., Bullmore, E. T., Williams, S. C., Van Amelsvoort, T., Robertson, D. M., et al. (2000). The functional neuroanatomy of social behaviour: changes in cerebral blood flow when people with autistic disorder process facial expressions. *Brain, 123 (Pt 11)*, 2203-2212.

Crow, T. J. (1980). Molecular pathology of schizophrenia: more than one disease process? *Br Med J, 280*(6207), 66-68.

Cullberg, J. (2003). Stressful life events preceding the first onset of psychosis. An explorative study. *Nord J Psychiatry, 57*(3), 209-214.

Cuthbert, B. N., Schupp, H. T., Bradley, M. M., Birbaumer, N., & Lang, P. J. (2000). Brain potentials in affective picture processing: covariation with autonomic arousal and affective report. *Biol Psychol, 52*(2), 95-111.

Damasio, H., Grabowski, T., Frank, R., Galaburda, A. M., & Damasio, A. R. (1994). The return of Phineas Gage: clues about the brain from the skull of a famous patient. *Science, 264*(5162), 1102-1105.

Darwin, C., & Ekman, P. (1872). *The expression of the emotions in man and animals*. London: John Murray.

Davidson, R. A., Fedio, P., Smith, B. D., Aureille, E., & Martin, A. (1992). Lateralized mediation of arousal and habituation: differential bilateral electrodermal activity in unilateral temporal lobectomy patients. *Neuropsychologia, 30*(12), 1053-1063.

Davidson, R. J., & Irwin, W. (1999). The functional neuroanatomy of emotion and affective style. *Trends Cogn Sci, 3*(1), 11-21.

Davis, M. (1992). The role of the amygdala in the conditioned fear. In A. J.P. (Ed.), *The amygdala: Neurobiological aspects of emotion, memory, and mental dysfuntion* (pp. 255-395). New York: Wiley-Liss.

Davis, M. (1996). Differential roles of the amygdala and bed nucleus of the stria terminalis in conditioned fear and startle enhanced by corticotropin-relasing hormone. In T. Ono, B. L. McNaughton, S. Molotchnikoff, E. T. Rolls & H. Nishijo (Eds.), *Perception, memory and emotion: Frontiers in neuroscience* (pp. 525-548). Oxford: Elsevier.

Davis, M., Falls, W. A., Campeau, S., & Kim, M. (1993). Fear-potentiated startle: a neural and pharmacological analysis. *Behav Brain Res, 58*(1-2), 175-198.

Davis, M., Walker, D. L., & Lee, Y. (1999). Neurophysiology and neuropharmacology of startle and its affective modification. In A. H. Bohmelt (Ed.), *Startle modification: Implications for neuroscience, cognitive science, and clinical science* (pp. 95-113). New York: Cambridge University Press.

De Kloet, E. R., Rosenfeld, P., Van Eekelen, J. A., Sutanto, W., & Levine, S. (1988). Stress, glucocorticoids and development. *Prog Brain Res, 73*, 101-120.

Depue, R. A., & Collins, P. F. (1999). Neurobiology of the structure of personality: dopamine, facilitation of incentive motivation, and extraversion. *Behav Brain Sci, 22*(3), 491-517; discussion 518-469.

Derogatis, L. R., Lipman, R. S., Rickels, K., Uhlenhuth, E. H., & Covi, L. (1974). The Hopkins Symptom Checklist (HSCL): a self-report symptom inventory. *Behav Sci, 19*(1), 1-15.

Devinsky, O., Morrell, M. J., & Vogt, B. A. (1995). Contributions of anterior cingulate cortex to behaviour. *Brain, 118 (Pt 1)*, 279-306.

Diedrich, O., Nauman, E., Maier, S., & Becker, G. (1997). A frontal positive slow wave in the ERP associated with emotional slides. *Journal of Psychophysiology, 11*, 71-84.

Dill, D. L., Chu, J. A., Grob, M. C., & Eisen, S. V. (1991). The reliability of abuse history reports: a comparison of two inquiry formats. *Compr Psychiatry, 32*(2), 166-169.

Dolan, R. J., & Morris, J. S. (2000). The functional anatomy of innate and acquired fear: Persective from neuroscience. In R. D. Lane & L. Nadel (Eds.), *Cognitive Neuroscience of Emotion* (pp. 225-241). New York: Oxfrod University Press.

Edwards, J., Jackson, H. J., & Pattison, P. E. (2002). Emotion recognition via facial expression and affective prosody in schizophrenia: a methodological review. *Clin Psychol Rev, 22*(6), 789-832.

Eichenbaum, H., Otto, T., & Cohen, N. J. (1992). The hippocampus--what does it do? *Behav Neural Biol, 57*(1), 2-36.

Elbert, T. (1998). Neuromagnetism. In N. H. Andrä W. (Ed.), *Magnetism in Medicine* (pp. 190-261). Berlin: Willey-VCH.

Elbert, T. (2002). Organized violence and traumatic stress. On *Psychological Consequences of Organized Violence and Terror*. Cupramontana, Italy.

Elbert, T., & Rockstroh, B. (2003). Stress factors: The science of our flexible responses to an unpredictable world. *Nature, 421*, 477-478.

Elbert, T., & Rockstroh, B. (2004). *Abnormal neural communication and networks in psychiatric patients.* Paper presented at the International society for neuronal regulation.

Elklit, A., & Brink, O. (2004). Acute stress disorder as a predictor of post-traumatic stress disorder in physical assault victims. *J Interpers Violence, 19*(6), 709-726.

Ellason, J. W., & Ross, C. A. (1997). Childhood trauma and psychiatric symptoms. *Psychol Rep, 80*(2), 447-450.

Ellason, J. W., Ross, C. A., Sainton, K., & Mayran, L. W. (1996). Axis I and II comorbidity and childhood trauma history in chemical dependency. *Bull Menninger Clin, 60*(1), 39-51.

Embick, D., Hackl, M., Schaeffer, J., Kelepir, M., & Marantz, A. (2001). A magnetoencephalographic component whose latency reflects lexical frequency. *Brain Res Cogn Brain Res, 10*(3), 345-348.

Emery, N. J., & Amaral, D. G. (2000). The role of the amygdala in primate social cognition. In R. D. Lane & L. Nadel (Eds.), *Cognitive Neuroscience of Emotion* (pp. 156-191). New York: Oxford University Press.

Ettedgui, E., & Bridges, M. (1985). Posttraumatic stress disorder. *Psychiatr Clin North Am, 8*(1), 89-103.

Everitt, B. J., Cardinal, R. N., Parkinson, J. A., & Robbins, T. W. (2003). Appetitive behavior: impact of amygdala-dependent mechanisms of emotional learning. *Ann N Y Acad Sci, 985*, 233-250.

Fanselow, M. (1994). Neural organization of the defensive behavior system responsible for fear. *Psychonomic Bulletin & Review, 1*, 429-438.

Fell, J., Hauk, O., & Hinrichs, H. (2000). Linear inverse filtering improves spatial separation of nonlinear brain dynamics: a simulation study. *J Neurosci Methods, 98*(1), 49-56.

Felmingham, K. L., Bryant, R. A., & Gordon, E. (2003). Processing angry and neutral faces in post-traumatic stress disorder: an event-related potentials study. *Neuroreport, 14*(5), 777-780.

Felmingham, K. L., Bryant, R. A., Kendall, C., & Gordon, E. (2002). Event-related potential dysfunction in posttraumatic stress disorder: the role of numbing. *Psychiatry Res, 109*(2), 171-179.

Fergusson, D. M., Horwood, L. J., & Lynskey, M. T. (1996). Childhood sexual abuse and psychiatric disorder in young adulthood: II. Psychiatric outcomes of childhood sexual abuse. *J Am Acad Child Adolesc Psychiatry, 35*(10), 1365-1374.

Fernandez-Duque, D., & Posner, M. I. (2001). Brain imaging of attentional networks in normal and pathological states. *J Clin Exp Neuropsychol, 23*(1), 74-93.

Finamore, T. L., & Port, R. L. (2000). Developmental stress disrupts habituation but spares prepulse inhibition in young rats. *Physiol Behav, 69*(4-5), 527-530.

Foa, E. B. (1997). Trauma and women: course, predictors, and treatment. *J Clin Psychiatry, 58 Suppl 9*, 25-28.

Foa, E. B., & Kozak, M. J. (1986). Emotional processing of fear: exposure to corrective information. *Psychol Bull, 99*(1), 20-35.

Foa, E. B., Riggs, D. S., & Gershuny, B. S. (1995). Arousal, numbing, and intrusion: symptom structure of PTSD following assault. *Am J Psychiatry, 152*(1), 116-120.

Foa, E. B., Steketee, G., & Rothbaum, B. O. (1989). Behavioural/cognitive conceptualization of post-traumatic stress disorder. *Behaviour Therapy, 20*, 155-176.

Friedman, M. J. (1997). Posttraumatic stress disorder. *J Clin Psychiatry, 58 Suppl 9*, 33-36.

Friedman, S., & Harrison, G. (1984). Sexual histories, attitudes, and behavior of schizophrenic and "normal" women. *Arch Sex Behav, 13*(6), 555-567.

Friston, K. J., Holmes, A. P., Worsley, K. J., Poline, J. B., & Frith, C. D. (1995). Statistical parametric maps in functional imaging: a general linear approach. *Hum Brain Mapp, 2*, 189-210.

Funayama, E. S., Grillon, C., Davis, M., & Phelps, E. A. (2001). A double dissociation in the affective modulation of startle in humans: effects of unilateral temporal lobectomy. *J Cogn Neurosci, 13*(6), 721-729.

Gallagher, M., Graham, P. W., & Holland, P. C. (1990). The amygdala central nucleus and appetitive Pavlovian conditioning: lesions impair one class of conditioned behavior. *J Neurosci, 10*(6), 1906-1911.

Garcia, R. (2001). Stress, hippocampal plasticity, and spatial learning. *Synapse, 40*(3), 180-183.

Gatchel, R. J., & Lang, P. J. (1973). Accuracy of psychophysical judgments and physiological response amplitude. *J Exp Psychol, 98*(1), 175-183.

Gauthier, I., Skudlarski, P., Gore, J. C., & Anderson, A. W. (2000). Expertise for cars and birds recruits brain areas involved in face recognition. *Nat Neurosci, 3*(2), 191-197.

Gearon, J. S., Kaltman, S. I., Brown, C., & Bellack, A. S. (2003). Traumatic life events and PTSD among women with substance use disorders and schizophrenia. *Psychiatr Serv, 54*(4), 523-528.

Geisser, S. (2003). The analysis of profile data--revisited. *Stat Med, 22*(21), 3337-3346.

George, M. S., Ketter, T. A., Parekh, P. I., Horwitz, B., Herscovitch, P., & Post, R. M. (1995). Brain activity during transient sadness and happiness in healthy women. *Am J Psychiatry, 152*(3), 341-351.

Geracioti, T. D., Jr., Baker, D. G., Ekhator, N. N., West, S. A., Hill, K. K., Bruce, A. B., et al. (2001). CSF norepinephrine concentrations in posttraumatic stress disorder. *Am J Psychiatry, 158*(8), 1227-1230.

Gerardi, R. J., Keane, T. M., Cahoon, B. J., & Klauminzer, G. W. (1994). An in vivo assessment of physiological arousal in posttraumatic stress disorder. *J Abnorm Psychol, 103*(4), 825-827.

Gerhards, F., Yehuda, R., Shoham, M., & Hellhammer, D. H. (1997). Abnormal cerebral laterality in posttraumatic stress disorder. *Ann N Y Acad Sci, 821*, 482-485.

Gianaros, P. J., Van Der Veen, F. M., & Jennings, J. R. (2004). Regional cerebral blood flow correlates with heart period and high-frequency heart period variability during working-memory tasks: Implications for the cortical and subcortical regulation of cardiac autonomic activity. *Psychophysiology, 41*(4), 521-530.

Gillette, G. M., Skinner, R. D., Rasco, L. M., Fielstein, E. M., Davis, D. H., Pawelak, J. E., et al. (1997). Combat veterans with posttraumatic stress disorder exhibit decreased habituation of the P1 midlatency auditory evoked potential. *Life Sci, 61*(14), 1421-1434.

Gladstone, G., Parker, G., Wilhelm, K., Mitchell, P., & Austin, M. P. (1999). Characteristics of depressed patients who report childhood sexual abuse. *Am J Psychiatry, 156*(3), 431-437.

Goff, D. C., Brotman, A. W., Kindlon, D., Waites, M., & Amico, E. (1991). The delusion of possession in chronically psychotic patients. *J Nerv Ment Dis, 179*(9), 567-571.

Goldsmith, H. H., Gottesman, II, & Lemery, K. S. (1997). Epigenetic approaches to developmental psychopathology. *Dev Psychopathol, 9*(2), 365-387.

Golier, J. A., Yehuda, R., Bierer, L. M., Mitropoulou, V., New, A. S., Schmeidler, J., et al. (2003). The relationship of borderline personality disorder to posttraumatic stress disorder and traumatic events. *Am J Psychiatry, 160*(11), 2018-2024.

Goodman, L. A., Rosenberg, S. D., Mueser, K. T., & Drake, R. E. (1997). Physical and sexual assault history in women with serious mental illness: prevalence, correlates, treatment, and future research directions. *Schizophr Bull, 23*(4), 685-696.

Goodman, L. A., Thompson, K. M., Weinfurt, K., Corl, S., Acker, P., Mueser, K. T., et al. (1999). Reliability of reports of violent victimization and posttraumatic stress disorder among men and women with serious mental illness. *J Trauma Stress, 12*(4), 587-599.

Grave de Peralta-Menendez, R., & Gonzalez-Andino, S. L. (1998). A critical analysis of linear inverse solutions to the neuroelectromagnetic inverse problem. *IEEE Trans Biomed Eng, 45*(4), 440-448.

Grave de Peralta-Menendez, R., Hauk, O., Gonzalez-Andino, S. L., Vogt, H., & Michel, M. (1997). Linear inverse solutions with optimal resolution kernels aplied to electromagnetic tomography. *Human Brain Mapping, 5*, 454-467.

Green, B. L. (1994). Psychosocial research in traumatic stress: an update. *J Trauma Stress, 7*(3), 341-362.

Greenwald, M. K., Bradley, M. M., Cuthbert, B. N., & Lang, P. J. (1998). Startle potentiation: shock sensitization, aversive learning, and affective picture modulation. *Behav Neurosci, 112*(5), 1069-1079.

Grillon, C., Morgan, C. A., Southwick, S. M., Davis, M., & Charney, D. S. (1996). Baseline startle amplitude and prepulse inhibition in Vietnam veterans with posttraumatic stress disorder. *Psychiatry Res, 64*(3), 169-178.

Grillon, C., Southwick, S. M., & Charney, D. S. (1996). The psychobiological basis of posttraumatic stress disorder. *Mol Psychiatry, 1*(4), 278-297.

Grilo, C. M., Sanislow, C., Fehon, D. C., Martino, S., & McGlashan, T. H. (1999). Psychological and behavioral functioning in adolescent psychiatric inpatients who report histories of childhood abuse. *Am J Psychiatry, 156*(4), 538-543.

Gur, R. E., McGrath, C., Chan, R. M., Schroeder, L., Turner, T., Turetsky, B. I., et al. (2002). An fMRI study of facial emotion processing in patients with schizophrenia. *Am J Psychiatry, 159*(12), 1992-1999.

Haapasalo, J., & Hamalainen, T. (1996). Childhood family problems and current psychiatric problems among young violent and property offenders. *J Am Acad Child Adolesc Psychiatry, 35*(10), 1394-1401.

Haber, S. N., & McFarland, N. R. (1999). The concept of the ventral striatum in nonhuman primates. *Ann N Y Acad Sci, 877*, 33-48.

Halgren, E., Baudena, P., Heit, G., Clarke, J. M., Marinkovic, K., & Clarke, M. (1994). Spatio-temporal stages in face and word processing. I. Depth-recorded potentials in

the human occipital, temporal and parietal lobes [corrected]. *J Physiol Paris, 88*(1), 1-50.
Halgren, E., Raij, T., Marinkovic, K., Jousmaki, V., & Hari, R. (2000). Cognitive response profile of the human fusiform face area as determined by MEG. *Cereb Cortex, 10*(1), 69-81.
Hamalainen, M. S., Hari, R., Ilmoniemi, R., Knuutila, J., & Lounasmaa, O. V. (1993). Magnetoencephalography-theory, instrumentation, and applications to non-invasive studies of the working human brain. *Reviews of Modern Physics, 65*(2), 413-497.
Hamalainen, M. S., & Ilmoniemi, R. J. (1984). *Interpreting measured magnetic fields of the brain: estimates of current distributions* (Technical Report TKK-F-A599): Helsinky University of Technology.
Hamalainen, M. S., & Ilmoniemi, R. J. (1994). Interpreting magnetic fields of the brain: minimum norm estimates. *Med Biol Eng Comput, 32*(1), 35-42.
Hamner, M. B., Lorberbaum, J. P., & George, M. S. (1999). Potential role of the anterior cingulate cortex in PTSD: review and hypothesis. *Depress Anxiety, 9*(1), 1-14.
Hare, R. D., & Blevings, G. (1975). Defensive responses to phobic stimuli. *Biol Psychol, 3*(1), 1-13.
Hariri, A. R., Mattay, V. S., Tessitore, A., Fera, F., & Weinberger, D. R. (2003). Neocortical modulation of the amygdala response to fearful stimuli. *Biol Psychiatry, 53*(6), 494-501.
Harrison, C. A., & Kinner, S. A. (1998). Correlates of psychological distress following armed robbery. *J Trauma Stress, 11*(4), 787-798.
Hartley, T., Maguire, E. A., Spiers, H. J., & Burgess, N. (2003). The well-worn route and the path less traveled: distinct neural bases of route following and wayfinding in humans. *Neuron, 37*(5), 877-888.
Harvey, P. D., & Walker, E. F. (1987). *The positive and negative symptoms in psychosis: Description, research, and future directions*. Hilldale, NJ: Lawrence Erlbaum Associates.
Hauk, O., Berg, P., & Wienbruch, C. (1999a). *Independent estimates of brain activity obtained by linear estimation.* Paper presented at the Recent advantages in biomagnetism (Proceedings of the Eleventh Conference on Biomagnetism), Sendai.
Hauk, O., Keil, A., Elbert, T., & Muller, M. M. (2002). Comparison of data transformation procedures to enhance topographical accuracy in time-series analysis of the human EEG. *J Neurosci Methods, 113*(2), 111-122.
Heins, T., Gray, A., & Tennant, M. (1990). Persisting hallucinations following childhood sexual abuse. *Aust N Z J Psychiatry, 24*(4), 561-565.
Hendler, T., Rotshtein, P., & Hadar, U. (2001). Emotion-perception interplay in the visual cortex: "the eyes follow the heart". *Cell Mol Neurobiol, 21*(6), 733-752.
Hendler, T., Rotshtein, P., Yeshurun, Y., Weizmann, T., Kahn, I., Ben-Bashat, D., et al. (2003). Sensing the invisible: differential sensitivity of visual cortex and amygdala to traumatic context. *Neuroimage, 19*(3), 587-600.
Herman, J. L., Perry, J. C., & van der Kolk, B. A. (1989). Childhood trauma in borderline personality disorder. *Am J Psychiatry, 146*(4), 490-495.
Herman, J. L., & Schatzow, E. (1987). Recovery and verification of memories of childhood sexual trauma. *Psychoanalytic Psychology, 4*(1), 1-14.
Herman, J. L., & van der Kolk, B. (1987). Traumatic antecedents of borderline personality disorder. In B. van der Kolk (Ed.), *Psychological Trauma* (pp. 111-126). Washington, DC: American Psychiatric Press.
Hesbacher, P. T., Rickels, K., Morris, R. J., Newman, H., & Rosenfeld, H. (1980). Psychiatric illness in family practice. *J Clin Psychiatry, 41*(1), 6-10.

Hillyard, S. A., Vogel, E. K., & Luck, S. J. (1998). Sensory gain control (amplification) as a mechanism of selective attention: electrophysiological and neuroimaging evidence. *Philos Trans R Soc Lond B Biol Sci, 353*(1373), 1257-1270.

Hitchcock, J. M., Sananes, C. B., & Davis, M. (1989). Sensitization of the startle reflex by footshock: blockade by lesions of the central nucleus of the amygdala or its efferent pathway to the brainstem. *Behav Neurosci, 103*(3), 509-518.

Hodes, R. L., Cook, E. W., 3rd, & Lang, P. J. (1985). Individual differences in autonomic response: conditioned association or conditioned fear? *Psychophysiology, 22*(5), 545-560.

Hoehn-Saric, R., & McLeod, D. R. (1988). The peripheral sympathetic nervous system. Its role in normal and pathologic anxiety. *Psychiatr Clin North Am, 11*(2), 375-386.

Hoehn-Saric, R., & McLeod, D. R. (1993). Somatic manifestations of normal and pathological anxiety. In D. R. McLeod (Ed.), *Biology of Anxiety Disorders*. Washington: American PSychiatric Press.

Hoehn-Saric, R., McLeod, D. R., & Zimmerli, W. D. (1989). Somatic manifestations in women with generalized anxiety disorder. Psychophysiological responses to psychological stress. *Arch Gen Psychiatry, 46*(12), 1113-1119.

Holmes, A. P., Blair, R. C., Watson, J. D., & Ford, I. (1996). Nonparametric analysis of statistic images from functional mapping experiments. *J Cereb Blood Flow Metab, 16*(1), 7-22.

Hopfinger, J. B., Buonocore, M. H., & Mangun, G. R. (2000). The neural mechanisms of top-down attentional control. *Nat Neurosci, 3*(3), 284-291.

Hyun, M., Friedman, S. D., & Dunner, D. L. (2000). Relationship of childhood physical and sexual abuse to adult bipolar disorder. *Bipolar Disord, 2*(2), 131-135.

Ioannides, A. A. (2001). Real time human brain function: observations and inferences from single trial analysis of magnetoencephalographic signals. *Clin Electroencephalogr, 32*(3), 98-111.

Ito, T. A., Larsen, J. T., Smith, N. K., & Cacioppo, J. T. (1998). Negative information weighs more heavily on the brain: the negativity bias in evaluative categorizations. *J Pers Soc Psychol, 75*(4), 887-900.

Jacobson, A., & Richardson, B. (1987). Assault experiences of 100 psychiatric inpatients: evidence of the need for routine inquiry. *Am J Psychiatry, 144*(7), 908-913.

Junghofer, M., Bradley, M. M., Elbert, T. R., & Lan, P. J. (2001). Fleeting images: a new look at early emotion discrimination. *Psychophysiology, 38*(2), 175-178.

Junghofer, M., Elbert, T., Tucker, D. M., & Rockstroh, B. (2000). Statistical control of artifacts in dense array EEG/MEG studies. *Psychophysiology, 37*(4), 523-532.

Junghofer, M., Perlstein, W. M., Russmann, T. M., May, J. C., Cuthbert, B. N., Bradley, M. M., et al. (1999). *Arousal sensitive slow wave in high density EEG.* Paper presented at the SPR.

Kamphuis, J. H., & Emmelkamp, P. M. (1998). Crime-related trauma: psychological distress in victims of bankrobbery. *J Anxiety Disord, 12*(3), 199-208.

Kapp, B. S., Whalen, P. J., & Supple, W. F. (1992). Amygdaloid contributions to conditioned arousal and sensory information processing. In J. P. Aggleton (Ed.), *The Amygdala: Neurobiological aspects of emotion, memory, and mental dysfunction* (pp. 229-254). New York: Wiley-Liss.

Karama, S., Lecours, A. R., Leroux, J. M., Bourgouin, P., Beaudoin, G., Joubert, S., et al. (2002). Areas of brain activation in males and females during viewing of erotic film excerpts. *Hum Brain Mapp, 16*(1), 1-13.

Kastner, S., Pinsk, M. A., De Weerd, P., Desimone, R., & Ungerleider, L. G. (1999). Increased activity in human visual cortex during directed attention in the absence of visual stimulation. *Neuron, 22*(4), 751-761.

Kastner, S., & Ungerleider, L. G. (2001). The neural basis of biased competition in human visual cortex. *Neuropsychologia, 39*(12), 1263-1276.

Kawasaki, H., Kaufman, O., Damasio, H., Damasio, A. R., Granner, M., Bakken, H., et al. (2001). Single-neuron responses to emotional visual stimuli recorded in human ventral prefrontal cortex. *Nat Neurosci, 4*(1), 15-16.

Kay, S. R., Fiszbein, A., & Opler, L. A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull, 13*(2), 261-276.

Kayser, J., Tenke, C., Nordby, H., Hammerborg, D., Hugdahl, K., & Erdmann, G. (1997). Event-related potential (ERP) asymmetries to emotional stimuli in a visual half-field paradigm. *Psychophysiology, 34*(4), 414-426.

Keane, T. M., & Kaloupek, D. G. (1997). Comorbid psychiatric disorders in PTSD. Implications for research. *Ann N Y Acad Sci, 821*, 24-34.

Keane, T. M., Scott, W. O., Chavoya, G. A., Lamparski, D. M., & Fairbank, J. A. (1985). Social support in Vietnam veterans with posttraumatic stress disorder: a comparative analysis. *J Consult Clin Psychol, 53*(1), 95-102.

Keightley, M. L., Winocur, G., Graham, S. J., Mayberg, H. S., Hevenor, S. J., & Grady, C. L. (2003). An fMRI study investigating cognitive modulation of brain regions associated with emotional processing of visual stimuli. *Neuropsychologia, 41*(5), 585-596.

Keil, A., Bradley, M. M., Hauk, O., Rockstroh, B., Elbert, T., & Lang, P. J. (2002). Large-scale neural correlates of affective picture processing. *Psychophysiology, 39*(5), 641-649.

Keil, A., Gruber, T., Muller, M. M., Moratti, S., Stolarova, M., Bradley, M. M., et al. (2003). Early modulation of visual perception by emotional arousal: evidence from steady-state visual evoked brain potentials. *Cogn Affect Behav Neurosci, 3*(3), 195-206.

Keil, A., Muller, M. M., Gruber, T., Wienbruch, C., Stolarova, M., & Elbert, T. (2001). Effects of emotional arousal in the cerebral hemispheres: a study of oscillatory brain activity and event-related potentials. *Clin Neurophysiol, 112*(11), 2057-2068.

Kendler, K. S., Karkowski, L. M., & Prescott, C. A. (1999). Causal relationship between stressful life events and the onset of major depression. *Am J Psychiatry, 156*, 837-841.

Kessler, R. C., Sonnega, A., Bromet, E., Hughes, M., & Nelson, C. B. (1995). Posttraumatic stress disorder in the National Comorbidity Survey. *Arch Gen Psychiatry, 52*(12), 1048-1060.

Kiehl, K. A., Smith, A. M., Hare, R. D., Mendrek, A., Forster, B. B., Brink, J., et al. (2001). Limbic abnormalities in affective processing by criminal psychopaths as revealed by functional magnetic resonance imaging. *Biol Psychiatry, 50*(9), 677-684.

Kim, J. J., & Diamond, D. M. (2002). The stressed hippocampus, synaptic plasticity and lost memories. *Nat Rev Neurosci, 3*(6), 453-462.

Kimble, M., Kaloupek, D., Kaufman, M., & Deldin, P. (2000). Stimulus novelty differentially affects attentional allocation in PTSD. *Biol Psychiatry, 47*(10), 880-890.

Kirkpatrick, B., Buchanan, R. W., McKenney, P. D., Alphs, L. D., & Carpenter, W. T., Jr. (1989). The Schedule for the Deficit syndrome: an instrument for research in schizophrenia. *Psychiatry Res, 30*(2), 119-123.

Kohler, C. G., Gur, R. C., & Gur, R. E. (2000). Emotional processes in schizophrenia: a focus n affective states. In J. C. Borod (Ed.), *The neuropsychology of emotion* (pp. 432-455). New York: Oxford Universtiy Press.

Kounios, J., Litz, B., Kaloupek, D., Riggs, D., Knight, J., Weathers, F., et al. (1997). Electrophysiology of combat-related PTSD. *Ann N Y Acad Sci, 821*, 504-507.

Kuch, K., & Cox, B. J. (1992). Symptoms of PTSD in 124 survivors of the Holocaust. *Am J Psychiatry, 149*(3), 337-340.

Kunugi, H., Nanko, S., & Murray, R. M. (2001). Obstetric complications and schizophrenia: prenatal underdevelopment and subsequent neurodevelopmental impairment. *Br J Psychiatry Suppl, 40*, s25-29.

Ladd, C. O., Owens, M. J., & Nemeroff, C. B. (1996). Persistent changes in corticotropin-releasing factor neuronal systems induced by maternal deprivation. *Endocrinology, 137*(4), 1212-1218.

Lane, R. D., Chua, P. M., & Dolan, R. J. (1999). Common effects of emotional valence, arousal and attention on neural activation during visual processing of pictures. *Neuropsychologia, 37*(9), 989-997.

Lane, R. D., Fink, G. R., Chau, P. M., & Dolan, R. J. (1997). Neural activation during selective attention to subjective emotional responses. *Neuroreport, 8*(18), 3969-3972.

Lane, R. D., Reiman, E. M., Bradley, M. M., Lang, P. J., Ahern, G. L., Davidson, R. J., et al. (1997). Neuroanatomical correlates of pleasant and unpleasant emotion. *Neuropsychologia, 35*(11), 1437-1444.

Lang, A. J., Rodgers, C. S., Laffaye, C., Satz, L. E., Dresselhaus, T. R., & Stein, M. B. (2003). Sexual trauma, posttraumatic stress disorder, and health behavior. *Behav Med, 28*(4), 150-158.

Lang, P. J. (1968). Fear reduction and fear behavior: Problems in treating a contruct. In M. Shlien (Ed.), *Research in psychotherapy* (Vol. 3, pp. 90-102). Washington, DC: American Psychological Association.

Lang, P. J. (1979). Presidential address, 1978. A bio-informational theory of emotional imagery. *Psychophysiology, 16*(6), 495-512.

Lang, P. J. (1985). The cognitive psychophysiology of emotion. In A. Tuma, Maser JD (Ed.), *Anxiety and the Anxiety Disorders* (pp. 131-170). Hillsdale: NJ: Erlbaum.

Lang, P. J. (1994). The varieties of emotional experience: a meditation on James-Lange theory. *Psychol Rev, 101*(2), 211-221.

Lang, P. J. (1995). The emotion probe. Studies of motivation and attention. *Am Psychol, 50*(5), 372-385.

Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (1990). Emotion, attention, and the startle reflex. *Psychol Rev, 97*(3), 377-395.

Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (1998a). Emotion and motivation: measuring affective perception. *J Clin Neurophysiol, 15*(5), 397-408.

Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (1998b). Emotion, motivation, and anxiety: brain mechanisms and psychophysiology. *Biol Psychiatry, 44*(12), 1248-1263.

Lang, P. J., Bradley, M. M., Cuthbert, B. N., & Patrick, C. J. (1993). Emotion and psychopathology: a startle probe analysis. *Prog Exp Pers Psychopathol Res, 16*, 163-199.

Lang, P. J., Bradley, M. M., Fitzsimmons, J. R., Cuthbert, B. N., Scott, J. D., Moulder, B., et al. (1998). Emotional arousal and activation of the visual cortex: an fMRI analysis. *Psychophysiology, 35*(2), 199-210.

Lang, P. J., Bradley, M.M., Cuthbert, B.N. (1999). International Affective Picture System (IAPS): Instruction manual and affective ratings. On *Technical Report A-4*. Gainsville, FL: The Center for Research in Psychophysiology, University of Florida.

Lang, P. J., & Cuthbert, B. N. (1984). Affective information processing and the assessment of anxiety. *J Behav Assess, 6*(4), 369-395.

Lang, P. J., Davis, M., & Ohman, A. (2000). Fear and anxiety: animal models and human cognitive psychophysiology. *J Affect Disord, 61*(3), 137-159.

Lang, P. J., Fizsimmons, J. R., Bradley, M. M., Cuthbert, B. N., & Scott, J. D. (1996). Processing emotional pictures: Differential activation in primary visual cortex. *NeuroImage, 3*, S321.

Lang, P. J., Greenwald, M. K., Bradley, M. M., & Hamm, A. O. (1993). Looking at pictures: affective, facial, visceral, and behavioral reactions. *Psychophysiology, 30*(3), 261-273.

Lange, A., de Beurs, E., Dolan, C., Lachnit, T., Sjollema, S., & Hanewald, G. (1999). Long-term effects of childhood sexual abuse: objective and subjective characteristics of the abuse and psychopathology in later life. *J Nerv Ment Dis, 187*(3), 150-158.

Langeland, W., & Hartgers, C. (1998). Child sexual and physical abuse and alcoholism: a review. *J Stud Alcohol, 59*(3), 336-348.

Laurian, S., Bader, M., Lanares, J., & Oros, L. (1991). Topography of event-related potentials elicited by visual emotional stimuli. *Int J Psychophysiol, 10*(3), 231-238.

Le, T. H., Pardo, J. V., & Hu, X. (1998). 4 T-fMRI study of nonspatial shifting of selective attention: cerebellar and parietal contributions. *J Neurophysiol, 79*(3), 1535-1548.

LeDoux, J. E. (1992). Emotion and the amygdala. In A. J.P. (Ed.), *The amygdala: Neurobiological aspects of emotion, memory, and mental dysfuntion* (pp. 339-351). New York: Wiley-Liss.

LeDoux, J. E. (1995). Emotion: clues from the brain. *Annu Rev Psychol, 46*, 209-235.

LeDoux, J. E. (1996). *The emotional brain*. New York: Simon and Schuster.

LeDoux, J. E. (2000). Emotion circuits in the brain. *Annu Rev Neurosci, 23*, 155-184.

LeDoux, J. E., Cicchetti, P., Xagoraris, A., & Romanski, L. M. (1990). The lateral amygdaloid nucleus: sensory interface of the amygdala in fear conditioning. *J Neurosci, 10*(4), 1062-1069.

LeDoux, J. E., Farb, C., & Ruggiero, D. A. (1990). Topographic organization of neurons in the acoustic thalamus that project to the amygdala. *J Neurosci, 10*(4), 1043-1054.

Ledoux, J. E., & Muller, J. (1997). Emotional memory and psychopathology. *Philos Trans R Soc Lond B Biol Sci, 352*(1362), 1719-1726.

Lee, C. U., Shenton, M. E., Salisbury, D. F., Kasai, K., Onitsuka, T., Dickey, C. C., et al. (2002). Fusiform gyrus volume reduction in first-episode schizophrenia: a magnetic resonance imaging study. *Arch Gen Psychiatry, 59*(9), 775-781.

Levitan, R. D., Parikh, S. V., Lesage, A. D., Hegadoren, K. M., Adams, M., Kennedy, S. H., et al. (1998). Major depression in individuals with a history of childhood physical or sexual abuse: relationship to neurovegetative features, mania, and gender. *Am J Psychiatry, 155*(12), 1746-1752.

Lewine, J. D., Canive, J. M., Orrison, W. W., Jr., Edgar, C. J., Provencal, S. L., Davis, J. T., et al. (1997). Electrophysiological abnormalities in PTSD. *Ann N Y Acad Sci, 821*, 508-511.

Lewine, J. D., Thoma, R. J., Provencal, S. L., Edgar, C., Miller, G. A., & Canive, J. M. (2002). Abnormal stimulus-response intensity functions in posttraumatic stress disorder: an electrophysiological investigation. *Am J Psychiatry, 159*(10), 1689-1695.

Liberzon, I., Taylor, S. F., Amdur, R., Jung, T. D., Chamberlain, K. R., Minoshima, S., et al. (1999). Brain activation in PTSD in response to trauma-related stimuli. *Biol Psychiatry, 45*(7), 817-826.

Liotti, M., & Tucker, D. M. (1995). Emotion in assymetric corticolimbic networks. In R. J. Davidson & K. Hugdahl (Eds.), *Brain Assymetry* (pp. 389-423). Cambridge: MA: MIT Press.

Litz, B. T., & Keane, T. M. (1989). Information-processing in anxiety disorders: Application to the understanding of post-traumatic stress disorder. *Clinical Psychology Review, 9*(243-257).

Litz, B. T., Orsillo, S. M., Kaloupek, D., & Weathers, F. (2000). Emotional processing in posttraumatic stress disorder. *J Abnorm Psychol, 109*(1), 26-39.

Loue, S. (2002). The involuntary civil commitment of mentally ill persons in the United States and Romania: a comparative analysis. *J Leg Med, 23*(2), 211-250.

Lovallo, W. R., & Gerin, W. (2003). Psychophysiological reactivity: mechanisms and pathways to cardiovascular disease. *Psychosom Med, 65*(1), 36-45.

Luine, V., Villegas, M., Martinez, C., & McEwen, B. S. (1994). Stress-dependent impairments of spatial memory. Role of 5-HT. *Ann N Y Acad Sci, 746*, 403-404.

MacLeod, C., & Hagan, R. (1992). Individual differences in the selective processing of threatening information, and emotional responses to a stressful life event. *Behav Res Ther, 30*(2), 151-161.

Maercker, A., Michael, T., Fehm, L., Becker, E. S., & Margraf, J. (2004). Age of traumatisation as a predictor of post-traumatic stress disorder or major depression in young women. *Br J Psychiatry, 184*, 482-487.

Magarinos, A. M., Verdugo, J. M., & McEwen, B. S. (1997). Chronic stress alters synaptic terminal structure in hippocampus. *Proc Natl Acad Sci U S A, 94*(25), 14002-14008.

Maguire, E. A., Burgess, N., Donnett, J. G., Frackowiak, R. S., Frith, C. D., & O'Keefe, J. (1998). Knowing where and getting there: a human navigation network. *Science, 280*(5365), 921-924.

Mandal, M. K., Pandey, R., & Prasad, A. B. (1998). Facial expressions of emotions and schizophrenia: a review. *Schizophr Bull, 24*(3), 399-412.

Margo, G. M., & McLees, E. M. (1991). Further evidence for the significance of a childhood abuse history in psychiatric inpatients. *Compr Psychiatry, 32*(4), 362-366.

Markowitsch, H. J., Kessler, J., Van Der Ven, C., Weber-Luxenburger, G., Albers, M., & Heiss, W. D. (1998). Psychic trauma causing grossly reduced brain metabolism and cognitive deterioration. *Neuropsychologia, 36*(1), 77-82.

Martin, J. H. (1996). *Neuroanatomy: Text and Atlas*. Stamford, Connecticut: Appleton & Lange.

Matsuo, K., Kato, T., Taneichi, K., Matsumoto, A., Ohtani, T., Hamamoto, T., et al. (2003). Activation of the prefrontal cortex to trauma-related stimuli measured by near-infrared spectroscopy in posttraumatic stress disorder due to terrorism. *Psychophysiology, 40*(4), 492-500.

McEwen, B. S. (1998a). Protective and damaging effects of stress mediators. *N Engl J Med, 338*(3), 171-179.

McEwen, B. S. (1998b). Stress, adaptation, and disease. Allostasis and allostatic load. *Ann N Y Acad Sci, 840*, 33-44.

McEwen, B. S. (2002). Sex, stress and the hippocampus: allostasis, allostatic load and the aging process. *Neurobiol Aging, 23*(5), 921-939.

McEwen, B. S. (2004). Protection and damage from acute and chronic stress: allostasis and allostatic overload and relevance to the pathophysiology of psychiatric disorders. *Ann N Y Acad Sci, 1032*, 1-7.

McEwen, B. S., Conrad, C. D., Kuroda, Y., Frankfurt, M., Magarinos, A. M., & McKittrick, C. (1997). Prevention of stress-induced morphological and cognitive consequences. *Eur Neuropsychopharmacol, 7 Suppl 3*, S323-328.

McEwen, B. S., & Lasley, E. N. (2002). *The end of stress as we know it*: Joseph Henry Press/Dana Press.

McFall, M. E., Murburg, M. M., Ko, G. N., & Veith, R. C. (1990). Autonomic responses to stress in Vietnam combat veterans with posttraumatic stress disorder. *Biol Psychiatry, 27*(10), 1165-1175.

McFarlane, A. C., Bookless, C., & Air, T. (2001). Posttraumatic stress disorder in a general psychiatric inpatient population. *J Trauma Stress, 14*(4), 633-645.

McFarlane, A. C., Weber, D. L., & Clark, C. R. (1993). Abnormal stimulus processing in posttraumatic stress disorder. *Biol Psychiatry, 34*(5), 311-320.

McPherson, W. B., Newton, J. E., Ackerman, P., Oglesby, D. M., & Dykman, R. A. (1997). An event-related brain potential investigation of PTSD and PTSD symptoms in abused children. *Integr Physiol Behav Sci, 32*(1), 31-42.
Mollica, R. F. (2004). Surviving torture. *N Engl J Med, 351*(1), 5-7.
Mollica, R. F., Wyshak, G., de Marneffe, D., Khuon, F., & Lavelle, J. (1987). Indochinese versions of the Hopkins Symptom Checklist-25: a screening instrument for the psychiatric care of refugees. *Am J Psychiatry, 144*(4), 497-500.
Mollica, R. F., Wyshak, G., & Lavelle, J. (1987). The psychosocial impact of war trauma and torture on Southeast Asian refugees. *Am J Psychiatry, 144*(12), 1567-1572.
Moncrieff, J., Drummond, D. C., Candy, B., Checinski, K., & Farmer, R. (1996). Sexual abuse in people with alcohol problems. A study of the prevalence of sexual abuse and its relationship to drinking behaviour. *Br J Psychiatry, 169*(3), 355-360.
Monroe, S. M., & Simons, A. D. (1991). Diathesis-stress theories in the context of life stress research: implications for the depressive disorders. *Psychol Bull, 110*(3), 406-425.
Moratti, S., Keil, A., & Stolarova, M. (2004). Motivated attention in emotional picture processing is reflected by activity modulation in cortical attention networks. *Neuroimage, 21*(3), 954-964.
Morgan, C. A., 3rd, & Grillon, C. (1999). Abnormal mismatch negativity in women with sexual assault-related posttraumatic stress disorder. *Biol Psychiatry, 45*(7), 827-832.
Morgan, C. A., 3rd, Grillon, C., Lubin, H., & Southwick, S. M. (1997). Startle reflex abnormalities in women with sexual assault-related posttraumatic stress disorder. *Am J Psychiatry, 154*(8), 1076-1080.
Morgan, C. A., 3rd, Grillon, C., Southwick, S. M., Davis, M., & Charney, D. S. (1995). Fear-potentiated startle in posttraumatic stress disorder. *Biol Psychiatry, 38*(6), 378-385.
Morris, J. S., DeGelder, B., Weiskrantz, L., & Dolan, R. J. (2001). Differential extrageniculostriate and amygdala responses to presentation of emotional faces in a cortically blind field. *Brain, 124*(Pt 6), 1241-1252.
Morris, J. S., Friston, K. J., Buchel, C., Frith, C. D., Young, A. W., Calder, A. J., et al. (1998). A neuromodulatory role for the human amygdala in processing emotional facial expressions. *Brain, 121 (Pt 1)*, 47-57.
Morris, J. S., Frith, C. D., Perrett, D. I., Rowland, D., Young, A. W., Calder, A. J., et al. (1996). A differential neural response in the human amygdala to fearful and happy facial expressions. *Nature, 383*(6603), 812-815.
Morris, J. S., Ohman, A., & Dolan, R. J. (1998). Conscious and unconscious emotional learning in the human amygdala. *Nature, 393*(6684), 467-470.
Morris, J. S., Ohman, A., & Dolan, R. J. (1999). A subcortical pathway to the right amygdala mediating "unseen" fear. *Proc Natl Acad Sci U S A, 96*(4), 1680-1685.
Morrison, J. (1989). Childhood sexual histories of women with somatization disorder. *Am J Psychiatry, 146*(2), 239-241.
Muenzenmaier, K., Meyer, I., Struening, E., & Ferber, J. (1993). Childhood abuse and neglect among women outpatients with chronic mental illness. *Hosp Community Psychiatry, 44*(7), 666-670.
Mueser, K. T., Goodman, L. B., Trumbetta, S. L., Rosenberg, S. D., Osher, C., Vidaver, R., et al. (1998). Trauma and posttraumatic stress disorder in severe mental illness. *J Consult Clin Psychol, 66*(3), 493-499.
Mueser, K. T., & McGurk, S. R. (2004). Schizophrenia. *Lancet, 363*(9426), 2063-2072.
Mueser, K. T., Rosenberg, S. D., Goodman, L. A., & Trumbetta, S. L. (2002). Trauma, PTSD, and the course of severe mental illness: an interactive model. *Schizophr Res, 53*(1-2), 123-143.
Mueser, K. T., Salyers, M. P., Rosenberg, S. D., Goodman, L. A., Essock, S. M., Osher, F. C., et al. (2004). Interpersonal trauma and posttraumatic stress disorder in patients with

severe mental illness: demographic, clinical, and health correlates. *Schizophr Bull, 30*(1), 45-57.
Mulder, R. T., Beautrais, A. L., Joyce, P. R., & Fergusson, D. M. (1998). Relationship between dissociation, childhood sexual abuse, childhood physical abuse, and mental illness in a general population sample. *Am J Psychiatry, 155*(6), 806-811.
Mullen, P. E., Martin, J. L., Anderson, J. C., Romans, S. E., & Herbison, G. P. (1993). Childhood sexual abuse and mental health in adult life. *Br J Psychiatry, 163*, 721-732.
Nauta, W. J. (1971). The problem of the frontal lobe: a reinterpretation. *J Psychiatr Res, 8*(3), 167-187.
Nemery, B. (2004). Trauma and PTSD Symptoms in Rwanda. *Jama, 292*(17), 2082; author reply 2082-2083.
Neuner, F., Schauer, M., Karunakara, U., Klaschik, C., Robert, C., & Elbert, T. (2004). Psychological trauma and evidence for enhanced vulnerability for posttraumatic stress disorder through previous trauma among West Nile refugees. *BMC Psychiatry, 4*(1), 34.
Newport, D. J., & Nemeroff, C. B. (2000). Neurobiology of posttraumatic stress disorder. *Curr Opin Neurobiol, 10*(2), 211-218.
Newport, D. J., Stowe, Z. N., & Nemeroff, C. B. (2002). Parental depression: animal models of an adverse life event. *Am J Psychiatry, 159*(8), 1265-1283.
Neylan, T. C., Fletcher, D. J., Lenoci, M., McCallin, K., Weiss, D. S., Schoenfeld, F. B., et al. (1999). Sensory gating in chronic posttraumatic stress disorder: reduced auditory P50 suppression in combat veterans. *Biol Psychiatry, 46*(12), 1656-1664.
Nishith, P., Mechanic, M. B., & Resick, P. A. (2000). Prior interpersonal trauma: the contribution to current PTSD symptoms in female rape victims. *J Abnorm Psychol, 109*(1), 20-25.
Norman, R. M., & Malla, A. K. (1993). Stressful life events and schizophrenia. I: A review of the research. *Br J Psychiatry, 162*, 161-166.
Nutt, D. J., & Malizia, A. L. (2004). Structural and functional brain changes in posttraumatic stress disorder. *J Clin Psychiatry, 65 Suppl 1*, 11-17.
Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia, 9*(1), 97-113.
Orr, S. P. (1997). Psychophysiologic reactivity to trauma-related imagery in PTSD. Diagnostic and theoretical implications of recent findings. *Ann N Y Acad Sci, 821*, 114-124.
Orr, S. P., Lasko, N. B., Shalev, A. Y., & Pitman, R. K. (1995). Physiologic responses to loud tones in Vietnam veterans with posttraumatic stress disorder. *J Abnorm Psychol, 104*(1), 75-82.
Orr, S. P., Meyerhoff, J. L., Edwards, J. V., & Pitman, R. K. (1998). Heart rate and blood pressure resting levels and responses to generic stressors in Vietnam veterans with posttraumatic stress disorder. *J Trauma Stress, 11*(1), 155-164.
Orr, S. P., Pitman, R. K., Lasko, N. B., & Herz, L. R. (1993). Psychophysiological assessment of posttraumatic stress disorder imagery in World War II and Korean combat veterans. *J Abnorm Psychol, 102*(1), 152-159.
Paige, S. R., Reid, G. M., Allen, M. G., & Newton, J. E. (1990). Psychophysiological correlates of posttraumatic stress disorder in Vietnam veterans. *Biol Psychiatry, 27*(4), 419-430.
Palmer, R. L. (1992). Effects of childhood sexual abuse on adult mental health. *Br J Hosp Med, 48*(1), 9-10.
Palmer, R. L., Bramble, D., Metcalfe, M., Oppenheimer, R., & Smith, J. (1994). Childhood sexual experiences with adults: adult male psychiatric patients and general practice attenders. *Br J Psychiatry, 165*(5), 675-679.

Palmer, R. L., Coleman, L., Chaloner, D., Oppenheimer, R., & Smith, J. (1993). Childhood sexual experiences with adults. A comparison of reports by women psychiatric patients and general-practice attenders. *Br J Psychiatry, 163*, 499-504.

Palomba, D., Angrilli, A., & Mini, A. (1997). Visual evoked potentials, heart rate responses and memory to emotional pictorial stimuli. *Int J Psychophysiol, 27*(1), 55-67.

Paradiso, S., Andreasen, N. C., Crespo-Facorro, B., O'Leary, D. S., Watkins, G. L., Boles Ponto, L. L., et al. (2003). Emotions in unmedicated patients with schizophrenia during evaluation with positron emission tomography. *Am J Psychiatry, 160*(10), 1775-1783.

Paradiso, S., Robinson, R. G., Andreasen, N. C., Downhill, J. E., Davidson, R. J., Kirchner, P. T., et al. (1997). Emotional activation of limbic circuitry in elderly normal subjects in a PET study. *Am J Psychiatry, 154*(3), 384-389.

Paris, J. (1997). Childhood trauma as an etiological factor in the personality disorders. *J Personal Disord, 11*(1), 34-49.

Patrick, C. J., Cuthbert, B. N., & Lang, P. J. (1994). Emotion in the criminal psychopath: fear image processing. *J Abnorm Psychol, 103*(3), 523-534.

Pettigrew, J., & Burcham, J. (1997). Effects of childhood sexual abuse in adult female psychiatric patients. *Aust N Z J Psychiatry, 31*(2), 208-213.

Phillips, M. L., Williams, L., Senior, C., Bullmore, E. T., Brammer, M. J., Andrew, C., et al. (1999). A differential neural response to threatening and non-threatening negative facial expressions in paranoid and non-paranoid schizophrenics. *Psychiatry Res, 92*(1), 11-31.

Pissiota, A., Frans, O., Michelgard, A., Appel, L., Langstrom, B., Flaten, M. A., et al. (2003). Amygdala and anterior cingulate cortex activation during affective startle modulation: a PET study of fear. *Eur J Neurosci, 18*(5), 1325-1331.

Pitman, R. K., & Orr, S. P. (1990). Psychophysiology of post-traumatic stress disorder. In S. Gershon (Ed.), *New directions of in affective disorders*. New York: Springer Verlag.

Pitman, R. K., Orr, S. P., Forgue, D. F., de Jong, J. B., & Claiborn, J. M. (1987). Psychophysiologic assessment of posttraumatic stress disorder imagery in Vietnam combat veterans. *Arch Gen Psychiatry, 44*(11), 970-975.

Pitman, R. K., Orr, S. P., Shalev, A. Y., Metzger, L. J., & Mellman, T. A. (1999). Psychophysiological alterations in post-traumatic stress disorder. *Semin Clin Neuropsychiatry, 4*(4), 234-241.

Pitman, R. K., Shin, L. M., & Rauch, S. L. (2001). Investigating the pathogenesis of posttraumatic stress disorder with neuroimaging. *J Clin Psychiatry, 62 Suppl 17*, 47-54.

Plotsky, P. M., & Meaney, M. J. (1993). Early, postnatal experience alters hypothalamic corticotropin-releasing factor (CRF) mRNA, median eminence CRF content and stress-induced release in adult rats. *Brain Res Mol Brain Res, 18*(3), 195-200.

Poline, J. B., Worsley, K. J., Holmes, A. P., Frackowiak, R. S., & Friston, K. J. (1995). Estimating smoothness in statistical parametric maps: variability of p values. *J Comput Assist Tomogr, 19*(5), 788-796.

Porges, S. W. (1995). Orienting in a defensive world: mammalian modifications of our evolutionary heritage. A Polyvagal Theory. *Psychophysiology, 32*(4), 301-318.

Powell, R. A. (1994). Childhood abuse and psychosis. *Br J Psychiatry, 165*(6), 838-839.

Pribor, E. F., Yutzy, S. H., Dean, J. T., & Wetzel, R. D. (1993). Briquet's syndrome, dissociation, and abuse. *Am J Psychiatry, 150*(10), 1507-1511.

Pribram, K. H. (1970). Feelings and Emotions. In M. B. Arnold (Ed.), *THe Loyola symposium* (pp. 41-53). New York: Academic.

Priebe, S., Broker, M., & Gunkel, S. (1998). Involuntary admission and posttraumatic stress disorder symptoms in schizophrenia patients. *Compr Psychiatry, 39*(4), 220-224.

Prigerson, H. G., Maciejewski, P. K., & Rosenheck, R. A. (2001). Combat trauma: trauma with highest risk of delayed onset and unresolved posttraumatic stress disorder symptoms, unemployment, and abuse among men. *J Nerv Ment Dis, 189*(2), 99-108.

Pryce, C. R., Bettschen, D., & Feldon, J. (2001). Comparison of the effects of early handling and early deprivation on maternal care in the rat. *Dev Psychobiol, 38*(4), 239-251.

Pynoos, R. S., Ritzmann, R. F., Steinberg, A. M., Goenjian, A., & Prisecaru, I. (1996). A behavioral animal model of posttraumatic stress disorder featuring repeated exposure to situational reminders. *Biol Psychiatry, 39*(2), 129-134.

Radley, J. J., Sisti, H. M., Hao, J., Rocher, A. B., McCall, T., Hof, P. R., et al. (2004). Chronic behavioral stress induces apical dendritic reorganization in pyramidal neurons of the medial prefrontal cortex. *Neuroscience, 125*(1), 1-6.

Raine, A., Lencz, T., Bihrle, S., LaCasse, L., & Colletti, P. (2000). Reduced prefrontal gray matter volume and reduced autonomic activity in antisocial personality disorder. *Arch Gen Psychiatry, 57*(2), 119-127; discussion 128-119.

Rasmussen, K., & Jacobs, B. L. (1986). Single unit activity of locus coeruleus neurons in the freely moving cat. II. Conditioning and pharmacologic studies. *Brain Res, 371*(2), 335-344.

Rasmusson, A. M., & Charney, D. S. (1997). Animal models of relevance to PTSD. *Ann N Y Acad Sci, 821*, 332-351.

Rauch, S. L., Shin, L. M., Segal, E., Pitman, R. K., Carson, M. A., McMullin, K., et al. (2003). Selectively reduced regional cortical volumes in post-traumatic stress disorder. *Neuroreport, 14*(7), 913-916.

Rauch, S. L., van der Kolk, B. A., Fisler, R. E., Alpert, N. M., Orr, S. P., Savage, C. R., et al. (1996). A symptom provocation study of posttraumatic stress disorder using positron emission tomography and script-driven imagery. *Arch Gen Psychiatry, 53*(5), 380-387.

Rauch, S. L., Whalen, P. J., Shin, L. M., McInerney, S. C., Macklin, M. L., Lasko, N. B., et al. (2000). Exaggerated amygdala response to masked facial stimuli in posttraumatic stress disorder: a functional MRI study. *Biol Psychiatry, 47*(9), 769-776.

Read, J. (1997). Child abuse and psychosis: A literature review and implications for professional practice. *Professional Psychology: Research and Practice, 28*(5), 448-456.

Read, J. (1998). Child abuse and severity of disturbance among adult psychiatric inpatients. *Child Abuse Negl, 22*(5), 359-368.

Read, J., Agar, K., Argyle, N., & Aderhold, V. (2003). Sexual and physical abuse during childhood and adulthood as predictors of hallucinations, delusions and thought disorder. *Psychol Psychother, 76*(Pt 1), 1-22.

Read, J., & Argyle, N. (1999). Hallucinations, delusions, and thought disorder among adult psychiatric inpatients with a history of child abuse. *Psychiatr Serv, 50*(11), 1467-1472.

Read, J., Perry, B. D., Moskowitz, A., & Connolly, J. (2001). The contribution of early traumatic events to schizophrenia in some patients: a traumagenic neurodevelopmental model. *Psychiatry, 64*(4), 319-345.

Read, J., & Ross, C. A. (2003). Psychological trauma and psychosis: another reason why people diagnosed schizophrenic must be offered psychological therapies. *J Am Acad Psychoanal Dyn Psychiatry, 31*(1), 247-268.

Reiman, E. M., Lane, R. D., Ahern, G. L., Schwartz, G. E., Davidson, R. J., Friston, K. J., et al. (1997). Neuroanatomical correlates of externally and internally generated human emotion. *Am J Psychiatry, 154*(7), 918-925.

Resnick, S. G., Bond, G. R., & Mueser, K. T. (2003). Trauma and posttraumatic stress disorder in people with schizophrenia. *J Abnorm Psychol, 112*(3), 415-423.

Rickels, K., Garcia, C. R., Lipman, R. S., Derogatis, L. R., & Fisher, E. L. (1976). The Hopkins Symptom Checklist. Assessing emotional distress in obstetric-gynecologic practice. *Prim Care, 3*(4), 751-764.

Rolls, E. T. (1996). The orbitofrontal cortex. *Philos Trans R Soc Lond B Biol Sci, 351*(1346), 1433-1443; discussion 1443-1434.

Romanski, L. M., & LeDoux, J. E. (1992). Equipotentiality of thalamo-amygdala and thalamo-cortico-amygdala circuits in auditory fear conditioning. *J Neurosci, 12*(11), 4501-4509.

Rosenthal, R., & Rosnow, R. (1985). *Contrast analysis: Focused comparisons in the analysis of variance*. Cambridge: Cambridge University Press.

Ross, C. A., Anderson, G., & Clark, P. (1994). Childhood abuse and the positive symptoms of schizophrenia. *Hosp Community Psychiatry, 45*(5), 489-491.

Rotshtein, P., Malach, R., Hadar, U., Graif, M., & Hendler, T. (2001). Feeling or features: different sensitivity to emotion in high-order visual cortex and amygdala. *Neuron, 32*(4), 747-757.

Rushworth, M. F., Paus, T., & Sipila, P. K. (2001). Attention systems and the organization of the human parietal cortex. *J Neurosci, 21*(14), 5262-5271.

Saleptsi, E., Bichescu, D., Rockstroh, B., Neuner, F., Schauer, M., Studer, K., et al. (2004). Negative and positive childhood experiences across developmental periods in psychiatric patients with different diagnoses - an explorative study. *BMC Psychiatry, 4*(1), 40.

Sapolsky, R. M., & Meaney, M. J. (1986). Maturation of the adrenocortical stress response: neuroendocrine control mechanisms and the stress hyporesponsive period. *Brain Res, 396*(1), 64-76.

Sarvas, J. (1987). Basic mathematical and electromagnetic concepts of the biomagnetic inverse problem. *Phys Med Biol, 32*(1), 11-22.

Saver, J. L., & Damasio, A. R. (1991). Preserved access and processing of social knowledge in a patient with acquired sociopathy due to ventromedial frontal damage. *Neuropsychologia, 29*(12), 1241-1249.

Saxe, G. N., Chinman, G., Berkowitz, R., Hall, K., Lieberg, G., Schwartz, J., et al. (1994). Somatization in patients with dissociative disorders. *Am J Psychiatry, 151*(9), 1329-1334.

Schauer, M., Neuner, F., & Elbert, T. (2005). *Narrative Exposure Therapy (NET): A short-term intervention for traumatic stress disorders after war, terror, or torture*. Göttingen, Germany: Hogrefe.

Schlenker, R., Cohen, R., & Hopmann, G. (1995). Affective modulation of the startle reflex in schizophrenic patients. *Eur Arch Psychiatry Clin Neurosci, 245*(6), 309-318.

Schneider, F., Weiss, U., Kessler, C., Muller-Gartner, H. W., Posse, S., Salloum, J. B., et al. (1999). Subcortical correlates of differential classical conditioning of aversive emotional reactions in social phobia. *Biol Psychiatry, 45*(7), 863-871.

Schneider, F., Weiss, U., Kessler, C., Salloum, J. B., Posse, S., Grodd, W., et al. (1998). Differential amygdala activation in schizophrenia during sadness. *Schizophr Res, 34*(3), 133-142.

Schupp, H. T., Cuthbert, B. N., Bradley, M. M., Birbaumer, N., & Lang, P. J. (1997). Probe P3 and blinks: two measures of affective startle modulation. *Psychophysiology, 34*(1), 1-6.

Schupp, H. T., Cuthbert, B. N., Bradley, M. M., Cacioppo, J. T., Ito, T., & Lang, P. J. (2000). Affective picture processing: the late positive potential is modulated by motivational relevance. *Psychophysiology, 37*(2), 257-261.

Schupp, H. T., Junghofer, M., Weike, A. I., & Hamm, A. O. (2003). Attention and emotion: an ERP analysis of facilitated emotional stimulus processing. *Neuroreport, 14*(8), 1107-1110.

Schupp, H. T., Junghofer, M., Weike, A. I., & Hamm, A. O. (2004). The selective processing of briefly presented affective pictures: an ERP analysis. *Psychophysiology, 41*(3), 441-449.

Schupp, H. T., Ohman, A., Junghofer, M., Weike, A. I., Stockburger, J., & Hamm, A. O. (2004). The facilitated processing of threatening faces: an ERP analysis. *Emotion, 4*(2), 189-200.

Schutzwohl, M., & Maercker, A. (1999). Effects of varying diagnostic criteria for posttraumatic stress disorder are endorsing the concept of partial PTSD. *J Trauma Stress, 12*(1), 155-165.

Semple, W. E., Goyer, P. F., McCormick, R., Donovan, B., Muzic, R. F., Jr., Rugle, L., et al. (2000). Higher brain blood flow at amygdala and lower frontal cortex blood flow in PTSD patients with comorbid cocaine and alcohol abuse compared with normals. *Psychiatry, 63*(1), 65-74.

Shalev, A. Y., Orr, S. P., & Pitman, R. K. (1992). Psychophysiologic response during script-driven imagery as an outcome measure in posttraumatic stress disorder. *J Clin Psychiatry, 53*(9), 324-326.

Shalev, A. Y., Orr, S. P., & Pitman, R. K. (1993). Psychophysiologic assessment of traumatic imagery in Israeli civilian patients with posttraumatic stress disorder. *Am J Psychiatry, 150*(4), 620-624.

Shalev, A. Y., & Rogel-Fuchs, Y. (1993). Psychophysiology of the posttraumatic stress disorder: from sulfur fumes to behavioral genetics. *Psychosom Med, 55*(5), 413-423.

Shapiro, P. A., Sloan, R. P., Bagiella, E., Kuhl, J. P., Anjilvel, S., & Mann, J. J. (2000). Cerebral activation, hostility, and cardiovascular control during mental stress. *J Psychosom Res, 48*(4-5), 485-491.

Shaw, M. E., Strother, S. C., McFarlane, A. C., Morris, P., Anderson, J., Clark, C. R., et al. (2002). Abnormal functional connectivity in posttraumatic stress disorder. *Neuroimage, 15*(3), 661-674.

Shearer, S. L., Peters, C. P., Quaytman, M. S., & Ogden, R. L. (1990). Frequency and correlates of childhood sexual and physical abuse histories in adult female borderline inpatients. *Am J Psychiatry, 147*(2), 214-216.

Shin, L. M., McNally, R. J., Kosslyn, S. M., Thompson, W. L., Rauch, S. L., Alpert, N. M., et al. (1999). Regional cerebral blood flow during script-driven imagery in childhood sexual abuse-related PTSD: A PET investigation. *Am J Psychiatry, 156*(4), 575-584.

Shin, L. M., Whalen, P. J., Pitman, R. K., Bush, G., Macklin, M. L., Lasko, N. B., et al. (2001). An fMRI study of anterior cingulate function in posttraumatic stress disorder. *Biol Psychiatry, 50*(12), 932-942.

Shors, T. J., Miesegaes, G., Beylin, A., Zhao, M., Rydel, T., & Gould, E. (2001). Neurogenesis in the adult is involved in the formation of trace memories. *Nature, 410*(6826), 372-376.

Silove, D., Steel, Z., McGorry, P., Miles, V., & Drobny, J. (2002). The impact of torture on post-traumatic stress symptoms in war-affected Tamil refugees and immigrants. *Compr Psychiatry, 43*(1), 49-55.

Singh, K. D., Barnes, G. R., & Hillebrand, A. (2003). Group imaging of task-related changes in cortical synchronisation using nonparametric permutation testing. *Neuroimage, 19*(4), 1589-1601.

Skinner, R. D., Rasco, L. M., Fitzgerald, J., Karson, C. N., Matthew, M., Williams, D. K., et al. (1999). Reduced sensory gating of the P1 potential in rape victims and combat veterans with posttraumatic stress disorder. *Depress Anxiety, 9*(3), 122-130.

Sokolov, Y. N. (1963). *Perception and the conditioned reflex*. London: Pergamon Press.

Southwick, S. M., Bremner, D., Krystal, J. H., & Charney, D. S. (1994). Psychobiologic research in post-traumatic stress disorder. *Psychiatr Clin North Am, 17*(2), 251-264.

Southwick, S. M., Krystal, J. H., Bremner, J. D., Morgan, C. A., 3rd, Nicolaou, A. L., Nagy, L. M., et al. (1997). Noradrenergic and serotonergic function in posttraumatic stress disorder. *Arch Gen Psychiatry, 54*(8), 749-758.

Stanford, M. S., Vasterling, J. J., Mathias, C. W., Constans, J. I., & Houston, R. J. (2001). Impact of threat relevance on P3 event-related potentials in combat-related post-traumatic stress disorder. *Psychiatry Res, 102*(2), 125-137.

Stefanis, C. N., & Reisby, N. (1993). The involvement of the World Psychiatric Association in the issue of the political abuse of psychiatry. *Acta Psychiatr Scand Suppl, 370*, 14-18.

Streit, M., Ioannides, A., Sinnemann, T., Wolwer, W., Dammers, J., Zilles, K., et al. (2001). Disturbed facial affect recognition in patients with schizophrenia associated with hypoactivity in distributed brain regions: a magnetoencephalographic study. *Am J Psychiatry, 158*(9), 1429-1436.

Streit, M., Ioannides, A. A., Liu, L., Wolwer, W., Dammers, J., Gross, J., et al. (1999). Neurophysiological correlates of the recognition of facial expressions of emotion as revealed by magnetoencephalography. *Brain Res Cogn Brain Res, 7*(4), 481-491.

Streit, M., Wolwer, W., Brinkmeyer, J., Ihl, R., & Gaebel, W. (2001). EEG-correlates of facial affect recognition and categorisation of blurred faces in schizophrenic patients and healthy volunteers. *Schizophr Res, 49*(1-2), 145-155.

Stroink, G., Moshage, W., & Achenbach, S. (1998). Model data using distributed sources as source model; Imaging. In N. H. Andrä W. (Ed.), *Magnetism in Medicine* (pp. 150-153). Berlin: Willey-VCH.

Swett, C., Jr., Surrey, J., & Cohen, C. (1990). Sexual and physical abuse histories and psychiatric symptoms among male psychiatric outpatients. *Am J Psychiatry, 147*(5), 632-636.

Tarrier, N., Sommerfield, C., Pilgrim, H., & Humphreys, L. (1999). Cognitive therapy or imaginal exposure in the treatment of post-traumatic stress disorder. Twelve-month follow-up. *Br J Psychiatry, 175*, 571-575.

Taylor, S. F., Liberzon, I., Fig, L. M., Decker, L. R., Minoshima, S., & Koeppe, R. A. (1998). The effect of emotional content on visual recognition memory: a PET activation study. *Neuroimage, 8*(2), 188-197.

Taylor, S. F., Liberzon, I., & Koeppe, R. A. (2000). The effect of graded aversive stimuli on limbic and visual activation. *Neuropsychologia, 38*(10), 1415-1425.

Taylor, S. F., Phan, K. L., Decker, L. R., & Liberzon, I. (2003). Subjective rating of emotionally salient stimuli modulates neural activity. *Neuroimage, 18*(3), 650-659.

van der Kolk, B. from http://www.traumacenter.org/assessment.html

van der Kolk, B. A., & Fisler, R. E. (1994). Childhood abuse and neglect and loss of self-regulation. *Bull Menninger Clin, 58*(2), 145-168.

van der Kolk, B. A., Hostetler, A., Herron, N., & Fisler, R. E. (1994). Trauma and the development of borderline personality disorder. *Psychiatr Clin North Am, 17*(4), 715-730.

Vasterling, J. J., Duke, L. M., Brailey, K., Constans, J. I., Allain, A. N., Jr., & Sutker, P. B. (2002). Attention, learning, and memory performances and intellectual resources in Vietnam veterans: PTSD and no disorder comparisons. *Neuropsychology, 16*(1), 5-14.

Verger, P., Dab, W., Lamping, D. L., Loze, J. Y., Deschaseaux-Voinet, C., Abenhaim, L., et al. (2004). The psychological impact of terrorism: an epidemiologic study of posttraumatic stress disorder and associated factors in victims of the 1995-1996 bombings in France. *Am J Psychiatry, 161*(8), 1384-1389.

Vermetten, E., & Bremner, J. D. (2002). Circuits and systems in stress. II. Applications to neurobiology and treatment in posttraumatic stress disorder. *Depress Anxiety, 16*(1), 14-38.

Villarreal, G., & King, C. Y. (2001). Brain imaging in posttraumatic stress disorder. *Semin Clin Neuropsychiatry, 6*(2), 131-145.

Volz, M., Hamm, A. O., Kirsch, P., & Rey, E. R. (2003). Temporal course of emotional startle modulation in schizophrenia patients. *Int J Psychophysiol, 49*(2), 123-137.

Vrana, S. R., Spence, E. L., & Lang, P. J. (1988). The startle probe response: a new measure of emotion? *J Abnorm Psychol, 97*(4), 487-491.

Vuilleumier, P., Armony, J. L., Driver, J., & Dolan, R. J. (2001). Effects of attention and emotion on face processing in the human brain: an event-related fMRI study. *Neuron, 30*(3), 829-841.

Vyas, A., Mitra, R., Shankaranarayana Rao, B. S., & Chattarji, S. (2002). Chronic stress induces contrasting patterns of dendritic remodeling in hippocampal and amygdaloid neurons. *J Neurosci, 22*(15), 6810-6818.

Wagner, G. S., Engblom, H., Billgren, T., Carlsson, M., Hedstrom, E., Ugander, M., et al. (2001). A method for assembling a collaborative research team from multiple disciplines and academic centers to study the relationships between ECG estimation and MRI measurement of myocardial infarct size. *J Electrocardiol, 34 Suppl*, 1-6.

Walker, E. F., & Diforio, D. (1997). Schizophrenia: a neural diathesis-stress model. *Psychol Rev, 104*(4), 667-685.

Wessa, M., & Flor, H. (2002). [Posttraumatic stress disorder and trauma memory--a psychobiological perspective]. *Z Psychosom Med Psychother, 48*(1), 28-37.

Whalen, P. J., Bush, G., McNally, R. J., Wilhelm, S., McInerney, S. C., Jenike, M. A., et al. (1998). The emotional counting Stroop paradigm: a functional magnetic resonance imaging probe of the anterior cingulate affective division. *Biol Psychiatry, 44*(12), 1219-1228.

Whalen, P. J., Rauch, S. L., Etcoff, N. L., McInerney, S. C., Lee, M. B., & Jenike, M. A. (1998). Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. *J Neurosci, 18*(1), 411-418.

Wik, G., Fredrikson, M., Ericson, K., Eriksson, L., Stone-Elander, S., & Greitz, T. (1993). A functional cerebral response to frightening visual stimulation. *Psychiatry Res, 50*(1), 15-24.

Williams, J. M. G., Watts, F. N., MacLeod, C. M., & Mathews, A. (1988). *Cognitive psychology and emotional disorders*. Chichester: Wiley.

Williams, L. M., Das, P., Harris, A. W., Liddell, B. B., Brammer, M. J., Olivieri, G., et al. (2004). Dysregulation of arousal and amygdala-prefrontal systems in paranoid schizophrenia. *Am J Psychiatry, 161*(3), 480-489.

Wilson, A. E., Calhoun, K. S., & Bernat, J. A. (1999). Risk recognition and trauma-related symptoms among sexually revictimized women. *J Consult Clin Psychol, 67*(5), 705-710.

Windle, M., Windle, R. C., Scheidt, D. M., & Miller, G. B. (1995). Physical and sexual abuse and associated mental disorders among alcoholic inpatients. *Am J Psychiatry, 152*(9), 1322-1328.

Winokur, A., Winokur, D. F., Rickels, K., & Cox, D. S. (1984). Symptoms of emotional distress in a family planning service: stability over a four-week period. *Br J Psychiatry, 144*, 395-399.

Wright, C. I., Fischer, H., Whalen, P. J., McInerney, S. C., Shin, L. M., & Rauch, S. L. (2001). Differential prefrontal cortex and amygdala habituation to repeatedly presented emotional stimuli. *Neuroreport, 12*(2), 379-383.

Wurr, C. J., & Partridge, I. M. (1996). The prevalence of a history of childhood sexual abuse in an acute adult inpatient population. *Child Abuse Negl, 20*(9), 867-872.

Yamasue, H., Kasai, K., Iwanami, A., Ohtani, T., Yamada, H., Abe, O., et al. (2003). Voxel-based analysis of MRI reveals anterior cingulate gray-matter volume reduction in posttraumatic stress disorder due to terrorism. *Proc Natl Acad Sci U S A, 100*(15), 9039-9043.

Yank, G. R., Bentley, K. J., & Hargrove, D. S. (1993). The vulnerability-stress model of schizophrenia: advances in psychosocial treatment. *Am J Orthopsychiatry, 63*(1), 55-69.

Yehuda, R. (1997). Stress and glucocorticoid. *Science, 275*(5306), 1662-1663.

Yehuda, R., Golier, J. A., Halligan, S. L., Meaney, M., & Bierer, L. M. (2004). The ACTH response to dexamethasone in PTSD. *Am J Psychiatry, 161*(8), 1397-1403.

Yehuda, R., & McEwen, B. S. (2004). Protective and damaging effects of the biobehavioral stress response: cognitive, systemic and clinical aspects: ISPNE XXXIV meeting summary. *Psychoneuroendocrinology, 29*(9), 1212-1222.

Yehuda, R., McFarlane, A. C., & Shalev, A. Y. (1998). Predicting the development of posttraumatic stress disorder from the acute response to a traumatic event. *Biol Psychiatry, 44*(12), 1305-1313.

Young, A. W., Aggleton, J. P., Hellawell, D. J., Johnson, M., Broks, P., & Hanley, J. R. (1995). Face processing impairments after amygdalotomy. *Brain, 118 (Pt 1)*, 15-24.

Zahn, T. P., Grafman, J., & Tranel, D. (1999). Frontal lobe lesions and electrodermal activity: effects of significance. *Neuropsychologia, 37*(11), 1227-1241.

Zanarini, M. C., Gunderson, J. G., Marino, M. F., Schwartz, E. O., & Frankenburg, F. R. (1989). Childhood experiences of borderline patients. *Compr Psychiatry, 30*(1), 18-25.

Zanarini, M. C., Yong, L., Frankenburg, F. R., Hennen, J., Reich, D. B., Marino, M. F., et al. (2002). Severity of reported childhood sexual abuse and its relationship to severity of borderline psychopathology and psychosocial impairment among borderline inpatients. *J Nerv Ment Dis, 190*(6), 381-387.

Zubieta, J. K., Chinitz, J. A., Lombardi, U., Fig, L. M., Cameron, O. G., & Liberzon, I. (1999). Medial frontal cortex involvement in PTSD symptoms: a SPECT study. *J Psychiatr Res, 33*(3), 259-264.

Materials for Study I

Fragebogen zu traumatischen Lebenserfahrungen

Fragebogen-Nr:____Datum: ____________

Alter:_______Geschlecht:________

Beruf: ____

Anleitung: Mit diesem Fragebogen bitten wir Sie, Erfahrungen zu beschreiben, die Sie vielleicht als Kleinkind (im Alter von 0-6 Jahren), als Schulkind (Alter 7-12 Jahre), als Jugendliche(r) (Alter 13-18) oder als Erwachsene(r) gemacht haben. Geben Sie für jeden Punkt an in welchem Ausmaß er Ihre Erfahrung für jeden der Lebensabschnitte beschreibt. Die Skala enthält sowohl Häufigkeits- als auch Intensitätswörter; wählen Sie bitte die höchste Ihrer Erfahrung entsprechende Ziffer. Falls es Alterszeiträume gibt für die Sie eine Frage nicht beantworten können, kreuzen Sie bitte WN ("weiß nicht") an.

Kreuzen Sie die größte für Sie zutreffende Ziffer an	**0** = niemals oder überhaupt nicht **1** = selten oder ein klein wenig **2** = gelegentlich oder ziemlich **3** = oft oder sehr **WN** = weiß nicht

	Alter	**Stärke / Häufigkeit**
1. Ich habe mich immer sicher und behütet gefühlt.	0-6	0 1 2 3 WN
	7-12	0 1 2 3 WN
	13-18	0 1 2 3 WN
	erwachsen	0 1 2 3 WN
2. Ein Mitglied meiner Familie oder eine Pflegeperson sorgte immer dafür, daß ich morgens aufstand und zur Schule ging.	0-6	0 1 2 3 WN
	7-12	0 1 2 3 WN
	13-18	0 1 2 3 WN
3. Ich war wirklich gut in etwas (z.B. Sport, ein Hobby, in der Schule, Arbeit oder bei einer kreativen Tätigkeit).	0-6	0 1 2 3 WN
	7-12	0 1 2 3 WN
	13-18	0 1 2 3 WN
	erwachsen	0 1 2 3 WN
4. Ich hatte gute Freunde.	0-6	0 1 2 3 WN
	7-12	0 1 2 3 WN
	13-18	0 1 2 3 WN
	erwachsen	0 1 2 3 WN
5. Ich fühlte mich mindestens einem meiner Brüder oder Schwestern nahe.	0-6	0 1 2 3 WN
	7-12	0 1 2 3 WN

	13-18	0	1	2	3	WN
	erwachsen	0	1	2	3	WN

Kreuzen Sie die größte für Sie zutreffende Ziffer an

0 = niemals oder überhaupt nicht
1 = selten oder ein klein wenig
2 = gelegentlich oder ziemlich
3 = oft oder sehr
WN = weiß nicht

	Alter	**Stärke / Häufigkeit**				
6. Ein Mitglied meiner Familie hatte so viele Probleme hatte, daß sie/er sich wenig um mich kümmern konnte.	0-6	0	1	2	3	WN
	7-12	0	1	2	3	WN
	13-18	0	1	2	3	WN
	erwachsen	0	1	2	3	WN
7. Ich hatte das Gefühl, daß es niemanden interessierte, ob ich lebe oder sterbe.	0-6	0	1	2	3	WN
	7-12	0	1	2	3	WN
	13-18	0	1	2	3	WN
	erwachsen	0	1	2	3	WN
8. Wenn mich zuhause etwas quälte, gab es außerhalb meiner Familie eine Person, mit der ich darüber reden konnte.	0-6	0	1	2	3	WN
	7-12	0	1	2	3	WN
	13-18	0	1	2	3	WN
	erwachsen	0	1	2	3	WN
9. In meiner Familie gab es Geheimnisse, über die ich nichts wissen sollte.	0-6	0	1	2	3	WN
	7-12	0	1	2	3	WN
	13-18	0	1	2	3	WN
	erwachsen	0	1	2	3	WN
10. Meine Eltern vertrauten mir Dinge an, durch die ich mich unwohl fühlte.	0-6	0	1	2	3	WN
	7-12	0	1	2	3	WN
	13-18	0	1	2	3	WN
	erwachsen	0	1	2	3	WN
11. Meine Eltern waren geschieden oder getrennt.	0-6	Nein				Ja
	7-12	Nein				Ja
	13-18	Nein				Ja
	erwachsen	Nein				Ja
12. Ich lebte zu verschiedenen Zeiten bei verschiedenen Leuten (z.B. Verwandte oder Pflegeeltern)	0-6	0	1	2	3	WN
	7-12	0	1	2	3	WN
	13-18	0	1	2	3	WN
13. Ein Person starb, die mir wichtig war und die ich gern mochte.	0-6	Nein				Ja
	7-12	Nein				Ja
	13-18	Nein				Ja

	erwachsen	Nein				Ja

14. Ich hatte eine schwere Krankheit und/oder mußte ins Krankenhaus.	0-6	0	1	2	3	WN
	7-12	0	1	2	3	WN
	13-18	0	1	2	3	WN
	erwachsen	0	1	2	3	WN

Kreuzen Sie die größte für Sie zutreffende Ziffer an

0 = niemals oder überhaupt nicht
1 = selten oder ein klein wenig
2 = gelegentlich oder ziemlich
3 = oft oder sehr
WN = weiß nicht

	Alter	**Stärke / Häufigkeit**				
15. Ein Familienmitglied oder eine andere Person, die ich lieb hatte und die mir viel bedeutete, war sehr krank bzw. hatte einen Unfall und mußte ins Krankenhaus.	0-6	0	1	2	3	WN
	7-12	0	1	2	3	WN
	13-18	0	1	2	3	WN
	erwachsen	0	1	2	3	WN
16. Ich erhielt die Nachricht, daß eine Person, die mir sehr wichtig war und die ich lieb hatte, schwer verletzt oder durch Gewalt in einem Unfall, Kampf oder Verbrechen getötet worden war.	0-6	0	1	2	3	WN
	7-12	0	1	2	3	WN
	13-18	0	1	2	3	WN
	erwachsen	0	1	2	3	WN
17. Ich konnte meinen Eltern nichts recht machen.	0-6	0	1	2	3	WN
	7-12	0	1	2	3	WN
	13-18	0	1	2	3	WN
	erwachsen	0	1	2	3	WN
18. Ich wurde von Familienmitglieder beschimpft und beleidigt.	0-6	0	1	2	3	WN
	7-12	0	1	2	3	WN
	13-18	0	1	2	3	WN
	erwachsen	0	1	2	3	WN
19. In meiner Familie wurden keine klaren Regeln eingehalten.	0-6	0	1	2	3	WN
	7-12	0	1	2	3	WN
	13-18	0	1	2	3	WN
	erwachsen	0	1	2	3	WN
20. Ich wurde ungerecht und unfair bestraft.	0-6	0	1	2	3	WN
	7-12	0	1	2	3	WN
	13-18	0	1	2	3	WN
	erwachsen	0	1	2	3	WN
21. Wenn meine Eltern stritten und kämpften, verletzten sie sich sogar körperlich.	0-6	0	1	2	3	WN
	7-12	0	1	2	3	WN
	13-18	0	1	2	3	WN
22. Ich verbrachte Zeit ausserhalb des Hauses und niemand wußte, wo ich war.	0-6	0	1	2	3	WN
	7-12	0	1	2	3	WN

	13-18	0 1 2 3 WN
	erwachsen	0 1 2 3 WN
23. Mitglieder meiner Familie verhielten sich unkontrolliert.	0-6	0 1 2 3 WN
	7-12	0 1 2 3 WN
	13-18	0 1 2 3 WN
	erwachsen	0 1 2 3 WN

Kreuzen Sie die größte für Sie zutreffende Ziffer an

0 = niemals oder überhaupt nicht
1 = selten oder ein klein wenig
2 = gelegentlich oder ziemlich
3 = oft oder sehr
WN = weiß nicht

	Alter	**Stärke / Häufigkeit**
24. Niemand wußte, was wirklich in meiner Familie passierte.	0-6	0 1 2 3 WN
	7-12	0 1 2 3 WN
	13-18	0 1 2 3 WN
	erwachsen	0 1 2 3 WN
25. Ich war Zeuge körperlicher Gewalt in meiner Familie.	0-6	0 1 2 3 WN
	7-12	0 1 2 3 WN
	13-18	0 1 2 3 WN
	erwachsen	0 1 2 3 WN
26. Ein Mitglied meiner Familie mußte wegen Gewaltanwendung ärztlich behandelt werden.	0-6	0 1 2 3 WN
	7-12	0 1 2 3 WN
	13-18	0 1 2 3 WN
	erwachsen	0 1 2 3 WN
27. Ein Mitglied meiner Familie hatte ein Problem mit Alkohol oder anderen Drogen.	0-6	0 1 2 3 WN
	7-12	0 1 2 3 WN
	13-18	0 1 2 3 WN
	erwachsen	0 1 2 3 WN
28. Ich habe mehr Alkohol und/oder andere Drogen genommen, als in Ordnung war.	0-6	0 1 2 3 WN
	7-12	0 1 2 3 WN
	13-18	0 1 2 3 WN
	erwachsen	0 1 2 3 WN
29. Meine Eltern oder Pflegepersonen, waren so mit Alkohol oder Drogen beschäftigt, daß sie sich nicht um mich kümmern konnten.	0-6	0 1 2 3 WN
	7-12	0 1 2 3 WN
	13-18	0 1 2 3 WN
30. Ich wurde durch ein Familienmitglied, oder eine andere Person, die mir wichtig war, geschlagen, geboxt oder getreten.	0-6	0 1 2 3 WN
	7-12	0 1 2 3 WN
	13-18	0 1 2 3 WN
	erwachsen	0 1 2 3 WN
31. Ich habe eine Situation erlebt, in der ich überzeugt	0-6	0 1 2 3 WN

war, daß ich verletzt oder sterben würde.	7-12	0 1 2 3 WN
	13-18	0 1 2 3 WN
	erwachsen	0 1 2 3 WN
32. Eine Person ausserhalb meiner Familie griff mich an.	0-6	0 1 2 3 WN
	7-12	0 1 2 3 WN
	13-18	0 1 2 3 WN
	erwachsen	0 1 2 3 WN

Kreuzen Sie die größte für Sie zutreffende Ziffer an	**0** = niemals oder überhaupt nicht
	1 = selten oder ein klein wenig
	2 = gelegentlich oder ziemlich
	3 = oft oder sehr
	WN = weiß nicht

	Alter	**Stärke / Häufigkeit**
33. Ich sah Leichen.	0-6	0 1 2 3 WN
	7-12	0 1 2 3 WN
	13-18	0 1 2 3 WN
	erwachsen	0 1 2 3 WN
34. Ich war in einen schweren Unfall verwickelt.	0-6	0 1 2 3 WN
	7-12	0 1 2 3 WN
	13-18	0 1 2 3 WN
	erwachsen	0 1 2 3 WN
35. Ich erlebte eine Naturkatastrophe.	0-6	0 1 2 3 WN
	7-12	0 1 2 3 WN
	13-18	0 1 2 3 WN
	erwachsen	0 1 2 3 WN
36. Ich sah sexuelle Dinge, die mich ängstigten.	0-6	0 1 2 3 WN
	7-12	0 1 2 3 WN
	13-18	0 1 2 3 WN
	erwachsen	0 1 2 3 WN
37. Eine Person, die älter war als ich, berührte mich gegen meinen Willen sexuell oder versuchte mich zu veranlassen ihn/sie sexuell zu berühren.	0-6	0 1 2 3 WN
	7-12	0 1 2 3 WN
	13-18	0 1 2 3 WN
	erwachsen	0 1 2 3 WN
38. Jemand zwang mich gegen meinen Willen zu Sex.	0-6	0 1 2 3 WN
	7-12	0 1 2 3 WN
	13-18	0 1 2 3 WN
	erwachsen	0 1 2 3 WN
39. Jemand drohte mir körperlichen Schaden an, falls ich mich gegen eine sexuelle Handlung wehren würde.	0-6	0 1 2 3 WN
	7-12	0 1 2 3 WN
	13-18	0 1 2 3 WN
	erwachsen	0 1 2 3 WN

40. Ich glaube, daß einer meiner Brüder oder Schwestern sexuell belästigt wurde.	0-6	0 1 2 3 WN
	7-12	0 1 2 3 WN
	13-18	0 1 2 3 WN
	erwachsen	0 1 2 3 WN

Kreuzen Sie die größte für Sie zutreffende Ziffer an

0 = niemals oder überhaupt nicht
1 = selten oder ein klein wenig
2 = gelegentlich oder ziemlich
3 = oft oder sehr
WN = weiß nicht

	Alter	**Stärke / Häufigkeit**
41. Ich hatte ein sehr ängstigendes oder verletzendes Erlebnis, in dem ich große Angst, Hilflosigkeit oder großen Schrecken verspürte.	0-6	0 1 2 3 WN
	7-12	0 1 2 3 WN
	13-18	0 1 2 3 WN
	erwachsen	0 1 2 3 WN
42. Ich habe das Gefühl, daß ich etwas Schreckliches erlebt habe, ich kann mich aber nicht erinnern, was das war.	0-6	0 1 2 3 WN
	7-12	0 1 2 3 WN
	13-18	0 1 2 3 WN
	erwachsen	0 1 2 3 WN

	Stärke
43 Wie anstrengend war es für Sie, diese Fragen zu beantworten?	0 1 2 3 WN

Materials for Study II & III

IAPS Pictures used in the experiment (normative pleasure and arousal ratings for individual slides).

PLEASANT PICTURES

Description	IAPS slide Number	pleasure	arousal
Adult	2000	6.51	3.32
Adult	2020	5.68	3.34
Baby	2070	8.17	4.51
Girls	2091	7.68	4.51
Father	2165	7.63	4.55
Mother	2311	7.54	4.42
Family	2340	8.03	4.90
Romance	4599	7.12	5.69
Erotic Couple	4653	6.56	5.83
Erotic Couple	4658	6.62	6.47
Erotic Couple	4680	7.25	6.02
Erotic Couple	4687	6.87	6.51
NEUTRAL PICTURES			
Man	2190	4.83	2.41
NeutMan	2214	5.01	3.46
NeutMan	2215	4.63	3.38
Male Face	2220	5.03	4.93
Sad Face	2230	4.53	4.13
Woman	2372	5.48	4.09
Girl	2381	5.25	3.04
Secretary	2383	4.72	3.41
NeutGirl	2440	4.49	2.63
Elderly Man	2480	4.77	2.66
Tourist	2850	5.22	3.00
Office	7550	5.27	3.95
UNPLEASANT PICTURES			
Angry Face	2110	3.71	4.53
Angry Face	2120	3.34	5.18
Hospital	2205	1.95	4.53
Crying Boy	2900	2.45	5.09
Abduction	6312	2.48	6.37
Attack	6350	1.90	7.29
Attack	6510	2.46	6.96
Attack	6540	2.19	6.83
Attack	6550	2.73	7.09
Attack	6560	2.16	6.53
Attack	6561	3.16	4.99
Suicide	6570	2.54	6.12