

**EEG Asymmetries in Survivors of Severe Motor Accidents:
Association with Posttraumatic Stress Disorder and its Treatment
as well as Posttraumatic Growth**

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List of Papers

This dissertation is based on the following papers, which will be referred to in the text by their Roman numerals.

- I. Rabe, S., Beauducel, A., Zoellner, T., Maercker, A., & Karl, A. (2006). Regional brain electrical activity in posttraumatic stress disorder after motor vehicle accident. *Journal of Abnormal Psychology, 115*(4), 687-698.
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- III. Rabe, S., Zoellner, T., Maercker, A., & Karl, A. (2006). Neural correlates of posttraumatic growth after severe motor vehicle accidents. *Journal of Consulting and Clinical Psychology, 74*(5), 880-886.

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1 Overview

Severe motor vehicle accidents (MVAs) represent one of the most often occurring psychological traumas, and are a leading cause of Posttraumatic Stress Disorder (PTSD). However, not all persons develop PTSD after traumatic events and a great proportion of patients who show symptoms initially recover over time. This has stimulated research of psychological and biological factors that explain development and maintenance of the disorder. Fortunately, this highly distressing condition can be effectively treated, e.g. via cognitive behavioral therapy (CBT). However, brain mechanisms underlying changes due to psychological therapy in PTSD are almost unknown (Roffman, Marci, Glick, Dougherty, & Rauch, 2005). On the other hand there are observations of positive changes following trauma called Posttraumatic Growth (PTG), which have stimulated research of associated psychological processes and factors. However, there is a lack of research about the relation of biological variables (e.g. measures of brain function) and PTG.

Theories of brain asymmetry and emotion (Davidson, 1998b, 2004b; Heller, Koven, & Miller, 2003) propose that asymmetries of brain activation are related to certain features of human emotion (e.g. valence, approach or withdrawal tendencies, arousal). Whereas an enormous increase in the understanding of structural and functional abnormalities in PTSD could be achieved in the last decades due to neuroimaging research, there are still numerous unanswered questions. Especially, there is only little research explicitly examining activation asymmetries in PTSD. Furthermore, as mentioned, research is sparse investigating alterations of brain function that are associated with successful psychological treatment of PTSD. Finally, there is no published study examining how measures of brain function are related to PTG.

This thesis presents 3 studies investigating electroencephalographic (EEG) asymmetries in survivors of severe motor vehicle accidents. The first part of the thesis (chapter 2) is devoted to a literature review about description (chapter 2.1), epidemiology (chapter 2.2 and 2.3), risk factors (chapter 2.4), psychological theories (chapter 2.5), biological mechanisms particularly neuroimaging findings (chapter 2.6), and treatment of PTSD (chapter 2.7.). Chapter 2.8 gives a short review on definition and research of Posttraumatic Growth. Chapter 2.9 provides an overview of models and research regarding brain asymmetry and emotion.

In chapter 3.1, a study is presented that investigated hemispheric asymmetries (EEG alpha) among MVA survivors with PTSD, with subsyndromal PTSD, and without PTSD as well as non-exposed healthy controls during a baseline condition and in response to neutral, positive, negative, and trauma-related pictures (study I). Next, the findings of study II are presented (chapter 3.2). This study examined the effect of cognitive behavioral therapy on measures of EEG activity. Therefore, EEG activity before and after CBT in comparison to an assessment only Wait-list condition was measured. In chapter 3.3 a correlational study (study III) is presented that examined the relationship between frontal brain asymmetry and self-reported posttraumatic growth after severe MVAs .

Finally, in chapter 4 the findings are summarized and discussed with respect to (1) the state/trait debate in frontal asymmetry research and (2) current psychological theories of PTSD and PTG. In addition, the use of neuroscientific research for psychotherapy is discussed. Suggestions are presented for future goals for “brain” research of PTSD and treatment of PTSD.

2 General Introduction

2.1 Definition and description of PTSD

Clinicians have long noted that traumatic events can lead to psychological disturbance. At the end of the nineteenth and the beginning of the twentieth centuries, railway disasters, the World Wars, and later the Holocaust, the atom bombs on Hiroshima & Nagasaki and to a great extent the Vietnam War prompted systematic descriptions of the symptoms associated with traumatic stress reactions (van der Kolk, Weisaeth, & van der Hart, 1996; Wilson, 1994). Names for these syndromes have been traumatic neurosis, Schreckneurose (i.e. fright neurosis), Renten neurose (i.e. compensation neurosis), combat neurosis, shell-shock, survivor syndrome, or operational fatigue.

Intensive research on the psychological consequences of the Vietnam War and the need for a better treatment of Vietnam veterans resulted in the introduction of posttraumatic stress disorder (PTSD) as a diagnostic category into the 3rd version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III, APA, 1980). For the first time there were criteria for diagnosis of PTSD. In its initial DSM-III formulation, a traumatic event was conceptualized as a catastrophic stressor that was outside the range of usual human experience. Thus, it was acknowledged that the etiological agent of PTSD was outside the individual but not that PTSD symptoms represented an individual weakness. The DSM-III diagnostic criteria for PTSD were revised in DSM-III-R (APA, 1987) and DSM-IV (APA, 1994). The main difference of the DSM-IV definition of PTSD from the two earlier DSM definitions is the stressor criterion. It is defined by two parts: the first part (Criterion A1) defines the range of traumatic events, which has broadened compared to the earlier versions including death of a loved one or being diagnosed with a life-threatening illness. The second part (Criterion A2) defines the person's emotional response (see Box 1) which emphasizes that people may respond differently to similar traumatic events. Core features of PTSD are 3 groups of symptoms: Criterion B: reexperiencing the trauma; Criterion C: avoidance of thoughts or situations associated with the traumatic event and numbing of affect; and Criterion D: symptoms of hyperarousal (for an exact descriptions of the DSM-IV symptoms please see Box 1). However, the current definition of PTSD has also been criticized (see reviews McHugh & Treisman, 2007; Rosen & Lilienfeld, 2008; Rosen, Spitzer, & McHugh, 2008; Wittchen, Gloster, Beesdo, Schonfeld, & Perkonigg, 2009).

Box 1: The diagnostic criteria for PTSD according to the DSM-IV

A Exposure to a traumatic event in which both of the following have been present:

- 1 The person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others
- 2 The person's response involved intense fear, helplessness, or horror.

B Reexperiencing of the traumatic event in one (or more) of the following ways:

- 1 Recurrent and intrusive distressing recollections of the event (images, thoughts, or perceptions)
- 2 Recurrent distressing dreams of the event.
- 3 Acting or feeling as if the traumatic event were recurring (includes a sense of reliving the experience, illusions, hallucinations, and dissociative flashback episodes)
- 4 Intense psychological distress at exposure to internal or external cues of the traumatic event.
- 5 Physiological reactivity on exposure to internal or external cues of the traumatic event.

C Avoidance and numbing of general responsiveness, as indicated by three (or more) of the following:

- 1 Efforts to avoid thoughts, feelings, or conversations associated with the trauma
- 2 Efforts to avoid activities, places, or people that arouse recollections of the trauma
- 3 Inability to recall an important aspect of the trauma
- 4 Markedly diminished interest or participation in significant activities
- 5 Feeling of detachment or estrangement from others
- 6 Restricted range of affect (e.g., unable to have loving feelings)
- 7 Sense of a foreshortened future

D Increased arousal, as indicated by two (or more) of the following:

- 1 Difficulty falling or staying asleep
- 2 Irritability or outbursts of anger
- 3 Difficulty concentrating
- 4 Hypervigilance
- 5 Exaggerated startle response

E Duration of the disturbance (symptoms in Criteria B, C, and D) is more than one month.

F Clinically significant distress or impairment in social, occupational, or other important areas of functioning

There are three subtypes of PTSD as defined in the DSM-IV. The first is called “acute PTSD” with duration of symptoms less than 3 months. The second subtype is “chronic PTSD” with symptom duration of more than 3 months. The third subtype is termed “delayed onset PTSD” which corresponds to an onset of symptoms at least 6 months following the traumatic event (for review see Andrews, Brewin, Philpott, & Stewart, 2007). Within one month after the traumatic experience, traumatized persons may meet the diagnostic criteria for acute stress disorder, which is associated with an increased risk for PTSD (Bryant, Harvey, Guthrie, & Moulds, 2000; Harvey & Bryant, 1998, 1999)

2.2 Prevalence, comorbidity and time course of PTSD

Prevalence. Epidemiological studies have documented that there is a high prevalence of exposure to traumatic events in the general population but a relatively small proportion develops chronic PTSD. Prevalence of trauma and PTSD has been investigated in large-scale epidemiologic surveys in the United States (U. S.) (Breslau, Davis, Andreski, & Peterson, 1991; Breslau et al., 1998; Helzer, Robins, & McEvoy, 1987; Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995; Norris, 1992; Resnick, Kilpatrick, Dansky, Saunders, & Best, 1993). Perhaps the most complete investigation of the general U.S. population is the National Comorbidity Survey (NCS, Kessler et al., 1995) using DSM-III-R criteria. They found a lifetime prevalence of exposure to at least one traumatic stressor of 56% and an overall lifetime prevalence of PTSD of 7.8% (5.0% of men 10.4% of women). The Detroit Area Survey (DAS, Breslau et al., 1998) found a prevalence rate for traumatic events of 90% and a lifetime PTSD prevalence rate of 9.2% in the U. S. population using DSM-IV criteria. Recently, the National Comorbidity Survey Replication (NCS-R, Kessler, Chiu, Demler, Merikangas, & Walters, 2005; Kessler & Merikangas, 2004) reported similar rates of lifetime PTSD (6,8%) using DSM-IV PTSD criteria.

Epidemiological studies have shown that the conditional risk (proportion of persons who develop PTSD following a traumatic event) is highest for so called “man made traumas” like rape (56%), combat (39%), and childhood physical abuse or physical attack (35%) (Kessler et al., 1995).

The European Study of the Epidemiology of Mental Disorders project (ESEMeD, Alonso et al., 2004) recently reported considerably lower rates of lifetime PTSD (1.9% overall, 0.9% for men, 2.9% of women). Similar results have been found in representative samples in Germany with lifetime PTSD prevalence rate of 1.3% (1% for men and 2.2 % for women) in a young cohort (age: 14-24 years) of Munich citizens (Perkonigg, Kessler, Storz, & Wittchen, 2000). However, the conditional probability for a PTSD diagnosis after a traumatic event was similar to U.S. populations, because the trauma prevalence rate was considerably lower in Germany (21.4%). Similar results have been found by Maercker, Michael, Fehm, Becker, and Margraf (2004) in a representative sample of young females in Dresden (Germany). In contrast to Europe and America, PTSD prevalence rates tend to be higher in less economically developed countries like Mexico (Norris et al., 2003) or Palestine (Punamaki, Komproe, Qouta, Elmasri, & de Jong, 2005) possibly mainly because of a greater number of highly stressful traumatic events.

Comorbidity. Epidemiological surveys have consistently found that PTSD is accompanied by one or more comorbid psychiatric disorders in more than 80% of the cases (Creamer, Burgess, & McFarlane, 2001; Kessler et al., 1995; Perkonig et al., 2000). Among the most prevalent comorbid disorders were major depression, alcohol, drug, or nicotine abuse/dependence, and anxiety disorders like simple phobia, social phobia, and agoraphobia with or without panic disorder. Furthermore, chronic pain has been found to be associated with PTSD (Asmundson, Coons, Taylor, & Katz, 2002; Liedl & Knaevelsrud, 2008).

Time course. Analysis of retrospective data in the NCS and the DAS showed that about 30-40% of those who have acute onset of symptoms recover within 12 months and approximately 50% recover after 4 years. However, in more than 30% of cases PTSD symptoms persist for more than 10 years (Breslau et al., 1998; Kessler et al., 1995). Furthermore, it has been shown that PTSD has a high impact on health care and economic costs (Chan, Medicine, Air, & McFarlane, 2003; Green, 2004; Walker et al., 2003).

2.3 PTSD among MVA survivors

In 2008 there were more than 2 millions MVAs in Germany, of which 2.293.663 police noticed MVAs, of which 320.614 involved injuries. All together 409.047 persons were injured and 4477 died in 2008 (*Statistisches Jahrbuch 2008 für die Bundesrepublik Deutschland*, 2008).

The National Comorbidity Survey (Kessler et al., 1995) found that 25% of men and 14% of women experienced life-threatening accidents (including MVAs). The probability to develop PTSD after a life-threatening accident was similar between males (6.3%) and females (8.8%) (no statistical difference). Furthermore, life-threatening accidents were a leading cause of PTSD in men (12.1%) and women (5.1%). The DAS (Breslau et al., 1998) found that 28% of the sample experienced a serious car crash what resulted in a somewhat lower conditional risk for PTSD after severe MVA of about 2.3%. Recent epidemiological studies of young peoples in Germany (Maercker et al., 2004; Perkonig et al., 2000) have revealed lower rates (<10%) of serious accidents (including MVAs) and low probabilities of PTSD (< 2.5 %) after serious accidents.

Blanchard and Hickling (2004) summarized data across prospective studies in unselected samples of MVA survivors (mainly recruited in accident and emergency services). In newer (post 1996) studies they found substantial variability (range = 4.7% to 34%) in

PTSD prevalence rates at the first reassessments (Bryant et al., 2000; Ehlers, Mayou, & Bryant, 1998; Frommberger et al., 1998; Fuglsang, Moergeli, & Schnyder, 2004; Harvey & Bryant, 1998, 1999; Koren, Arnon, & Klein, 1999, 2001; Mayou, Bryant, & Ehlers, 2001; Mayou, Ehlers, & Bryant, 2002; Mayou, Tyndel, & Bryant, 1997; Ursano et al., 1999). Among those the study of Ehlers, Mayou, and Bryant (1998) is perhaps the most significant one, investigating prospectively a large sample of British MVA survivors (n = 967) who were attending an emergency clinic shortly after a MVA. They found a prevalence of DSM-IV defined PTSD of 23.1% after 3 months and 16.5% after 1 year. A follow up investigation of this sample found a prevalence of 11 % after 3 years (Mayou et al., 2002).

2.4 Risk factors for PTSD

Although many people experience traumatic events, not all persons develop PTSD. This has led to the search for risk factors for PTSD (Shalev, 1996), factors that may predict development and maintenance of PTSD (Brewin, Andrews, & Valentine, 2000). The search for these factors may be useful for our understanding of the etiology of PTSD and may give hints for prevention and therapy. The psychological response to a traumatic event is determined by the characteristics of both the event and the person involved. Risk factors can be divided into three categories (1) pre-trauma risk factors, (2) peri-trauma risk factors and trauma-specific risk factors, and (3) post-trauma risk factors. Two recent meta-analytic studies (Brewin et al., 2000; Ozer, Best, Lipsey, & Weiss, 2003) investigated diverse risk factors in PTSD. Furthermore, Blanchard and Hickling (2004) reviewed studies investigating risk factors among MVA survivors.

2.4.1 Pre-trauma risk factors

These factors relate to characteristics of the individual that existed before the traumatic event. It is important to discriminate between predispositions for exposure to traumatic events and factors that predispose a person for development of PTSD (Keane, Marshall, & Taft, 2006). Pre-existing factors that have been identified to represent predispositions for developing PTSD are demographic factors like age and gender, prior trauma, prior psychiatric disorders but also genetic factors.

Gender. Epidemiological studies in the community have found that men are more likely to be exposed to traumatic events whereas women are more likely to develop PTSD.

Even when controlling for gender differences in the type of traumas (e.g. sexual assault, a traumatic event with a great risk for later PTSD that is more common among women) women seem to be more vulnerable to develop PTSD (Breslau, 2002; Breslau et al., 1998; Frans, Rimmo, Aberg, & Fredrikson, 2005; Kessler et al., 1995; Perkonigg et al., 2000; Tolin & Foa, 2006 for review). However, others did not find large gender differences (Creamer et al., 2001). Brewin et al. (2000) found that the average weighted effect of gender across studies is small ($r = 0.13$). Among MVA survivors there were inconsistent findings with some studies reporting a greater risk for PTSD for women whereas other studies found that gender is not a significant predictor of PTSD (for review see Blanchard & Hickling, 2004). Clearly there is need for more work on this issue especially the psychological and biological mechanisms involved in these differences (Becker et al., 2007).

Age. Age at the time of the traumatic event has been hypothesized to be an important predictor for PTSD since vulnerability for traumatic stress seems to be increased in certain developmental stages like childhood, adolescence or higher age (Maercker, 1999). However, Brewin et al. (2000) found age to be only a very small predictor of PTSD (weighted average effect size $r = 0.06$) across 29 studies. Brewin et al. (2000) found that other demographic factors (lower socioeconomic status (SES), less education, and lower intelligence) are associated with risk of PTSD with similar rather small effect sizes (range $r = .10$ to $.18$).

Prior trauma. There is evidence that history of trauma and life adversity may sensitize people to later trauma and thus increase the risk for development of PTSD following a later trauma. Brewin et al. (2000) reported rather small effect sizes for history of childhood abuse ($r = .14$), history of childhood adversity ($r = .19$), or history of other trauma ($r = .12$). Accordingly, Ozer et al. (2003) found that prior trauma predicted PTSD subsequent to a later trauma ($r = .19$), with prior accidents having the lowest ($r = 0.12$) and non-combat interpersonal violence having the highest ($r = 0.27$) effect sizes.

Psychopathology prior to the trauma. In their meta-analysis Brewin et al. (2000) found that psychiatric history was only a small predictor for development of PTSD ($r = .11$). Similarly, Ozer et al. (2003) found a small effect size for prior psychological problems ($r = .17$), however with a somewhat higher value when only examining prior depression ($r = .32$). Furthermore, pre-trauma psychopathology has been consistently found to predict PTSD in MVA survivors (Cox, Kenardy, & Hendrikz, 2008).

Family psychiatric history, genetic, and biological factors. In both Brewin et al.'s (2000) and Ozer et al.'s (2003) meta-analyses, psychopathology in the family was found to

confer a small degree of risk for PTSD ($r = 0.13$ and 0.17 , respectively). In a large twin study ($n = 4,042$) of Vietnam veterans True et al. (1993) investigated monozygotic and dizygotic twins. They revealed that inheritance had a substantial influence on liability for PTSD symptoms with genetic factors accounting for 13 to 34% variance. Recent studies have validated shared genetic risk factors for PTSD and exposure to assaultive violence in both combat (Koenen et al., 2002) and noncombat (Stein, Jang, Taylor, Vernon, & Livesley, 2002) populations (Koenen, Nugent, & Amstadter, 2008; Nugent, Amstadter, & Koenen, 2008). Furthermore, there is an ongoing debate whether biological abnormalities (e.g. hippocampal volume, hormonal changes) in found in PTSD subjects are only a consequence or might also represent a risk factor for PTSD (see chapter 2.6).

Cognitive factors. There is an ongoing debate whether cognitive variables represent a consequence, symptom, or vulnerability factor of PTSD (Moore, 2009). There is some evidence that reduced *cognitive functioning* (e.g. low intelligence; reduced performance on measures of verbal memory) might be a preexisting risk factor for PTSD (Brewin et al., 2000; Brewin, Kleiner, Vasterling, & Field, 2007; Moore, 2009). Mainly based on theory (Ehlers & Clark, 2000; Foa & Rothbaum, 1998) trauma-related *appraisals* are importantly linked to PTSD symptoms and play a major role in maintenance of the disorder (see also next chapter). However, there is some evidence that negative appraisals may also be a preexisting risk factor of PTSD. In a very interesting study, Bryant and Guthrie (2007) found that negative appraisals about oneself predicted the development of PTSD 4 years later in a sample of firefighters. Furthermore, there is some preliminary evidence that difficulties in *autobiographical memory* are not only a consequence of trauma but might be a preexisting risk factor (Bryant, Sutherland, & Guthrie, 2007). In summary, preexisting negative appraisals, impaired retrieval of autobiographical memories, and decrements in verbal memory may represent trait-like cognitive phenomena that increase risk for development and maintenance of PTSD (Elwood, Hahn, Olatunji, & Williams, 2009; Moore, 2009).

2.4.2 Peri-trauma risk factors and trauma-specific risk factors

These risk factors are related to the properties of the traumatic event itself as well as the immediate response of the person. The importance of these factors has been acknowledged by including some of them into Criterion A of the DSM-IV PTSD criteria.

Trauma severity and injury severity among MVA victims. In their meta-analysis Brewin et al. (2000) found that greater trauma severity was related moderately ($r = .23$) to

development of subsequent PTSD. It has been suggested, that PTSD severity is not a simple, straightforward function of the severity of injury or of the traumatic event, but rather injury contributes to a heightened level of perceived threat (Koren, Hemel, & Klein, 2006; Koren, Norman, Cohen, Berman, & Klein, 2005). The majority of studies with MVA victims did not find injury severity to be a predictor of later PTSD (Blanchard & Hickling, 2004). However, there are great differences in study populations (e.g. only hospitalized victims) that might attenuate the range of injury severity scores (Blanchard & Hickling, 2004). Furthermore, other injury related variables have been found to predict maintenance of PTSD after MVAs like admittance to a hospital, length of hospitalization, or continuing physical problems and pain from the MVA (Ehlers, Mayou et al., 1998; Frommberger et al., 1998; Mayou et al., 2002; Otis, Keane, & Kerns, 2003).

The reaction to the traumatic event. In their meta-analysis Ozer et al. (2003) found that peritraumatic psychological processes are the strongest predictors of PTSD. Across 16 studies Ozer et al. (2003) found *peritraumatic dissociation* (e.g. feelings of emotional numbing, disconnection from one's body, altered sense of time) to be the strongest predictor of PTSD with a medium effect size of $r = .35$. Also among MVA victims this variable is the most consistent predictor of development and maintenance of PTSD (for review see Blanchard & Hickling, 2004). Related to this are findings that the presence of *Acute Stress Disorder* (ASD, which includes 3 or more dissociative symptoms) predicted later development of PTSD among MVA victims (Fuglsang et al., 2004; Harvey & Bryant, 1998, 1999).

Ozer et al. (2003) found that *perceived life threat* had a small to medium effect ($r = .26$) on development of PTSD. Among MVA victims this variable has been consistently found to predict development and maintenance of PTSD (e.g., Blanchard et al., 1997; Cox et al., 2008 for review; Dougall, Ursano, Posluszny, Fullerton, & Baum, 2001; Ehlers, Mayou et al., 1998; Mayou et al., 2002). Similarly, other negative *emotional responses* during or immediately after the traumatic event (e.g. fear, helplessness, horror, guilt, and shame) have also been found to predict moderately ($r = .26$) development of PTSD (Ozer et al., 2003).

In addition, prospective studies examined variables based on cognitive models of PTSD, including PTCI scores as well as appraisals about the trauma. Both studies assessed cognitive factors at 2 weeks post trauma and found that theoretically derived factors based on cognitive models significantly better predicted later PTSD symptoms beyond the effects of

initial trauma-related symptoms and other classical risk-factors (Ehring, Ehlers, & Glucksman, 2008; Kleim, Ehlers, & Glucksman, 2007).

Also *physiological responses* that accompanied emotional reactions to the trauma have been found to predict development of PTSD. Especially greater resting heart rate (e.g. Bryant, Creamer, O'Donnell, Silove, & McFarlane, 2008) measured immediately after the traumatic event has been found to predict development of PTSD although there are inconsistent results (for review see Bryant, 2006) .

2.4.3 Post-trauma risk factors.

Social support and additional life stress. The only post-trauma factors included in recent meta-analyses of risk factors for PTSD have been social support and additional life stress. Brewin et al. (2000) found less social support (weighted effect size of $r = .40$) and additional life stress ($r = .32$) to be the strongest predictors of PTSD. Ozer et al. (2003) reported a small to medium average effect size ($r = .28$) across 11 studies for social support. Interestingly, they found that the relationship between social support and PTSD symptoms was stronger in studies where more time elapsed since the traumatic event (e.g. > 3 years). Altogether, these results imply that symptoms and duration of PTSD may be more severe if there is a lack of support from family and/or community.

2.5 Psychological models of PTSD

There are many psychological processes that have been identified to be associated with PTSD such as: memory disturbances (e.g. autobiographical memory, working memory, verbal memory); deficits in attention (e.g. attentional biases, sustained attention); beliefs, appraisals and negative interpretations; cognitive and behavioral coping strategies (e.g. thought suppression, different kinds of avoidance, safety behaviors); affective reactions (e.g. fear, shame, guilt, anger); and rumination (for reviews see Brewin, 2008; Brewin & Holmes, 2003; Buckley, Blanchard, & Neill, 2000; Ehlers & Clark, 2000; Ehlers, Hackmann, & Michael, 2004; McNally, 2006; Moore, 2009). Most of these factors have not been regarded as classical „risk factors“ for PTSD but rather as consequences of trauma, although there is some preliminary evidence, that cognitive factors and memory disturbances may also represent preexisting risk factors for development of PTSD (see previous chapter). Psychological theories try to explain the mechanisms that lead to the development and maintenance of PTSD

symptoms by incorporating the above mentioned psychological processes. Furthermore, these models should give implications for treatment and should be empirically testable.

2.5.1 Early theories

Many different and often overlapping psychological models of PTSD have been described. There are some earlier psychological theories of PTSD that have influenced research and treatment of the disorder (for comprehensive review see Brewin & Holmes, 2003). For example early so-called “social-cognitive“ theories described mainly changes in prior beliefs about the self, the world, and the future and changes in relations to the social world (Bolton & Hill, 1996; Horowitz, 1986; Janoff-Bulman, 1992). Furthermore, altered “information processing” has been proposed to explain some major features of PTSD (Jones & Barlow, 1990). However, early theories explained only details of the complex disorder PTSD and were restricted by the small amount of published research on trauma at this time (Brewin & Holmes, 2003).

2.5.2 Cognitive behavioral models of PTSD

Conditioning model

The two-factor conditioning theory of Mowrer (1960) was originally developed to explain other anxiety disorders (e.g. specific phobias) and has later been proposed to explain clinical symptoms of PTSD (Keane, Fairbank, Caddell, Zimering, & Bender, 1985). According to this theory, in a first phase of classical fear conditioning, a neutral stimulus (e.g. car, street) is associated with an unconditioned stimulus (e.g. accident) that innately evokes fear. These now conditioned stimuli may trigger responses similar to the reactions at the traumatic event (e.g. fear). Through the process of stimulus generalization and higher order conditioning, a wide variety of associated stimuli may become triggers of distress (Keane et al., 1985; Keane & Kaloupek, 1982). In a second phase of operant conditioning, avoidance of the conditioned stimuli (e.g. avoidance of driving with cars) reduces fear in a short term but prevents extinction of fear and thus maintains and reinforces the conditioned reaction and avoidance behaviors. The conditioning approach explains many features of PTSD as the wide range of traumatic triggers, the emotional and physiological reactions elicited by these stimuli and the central role of behavioral avoidance in the maintenance of PTSD. However, it does not explain main features of PTSD like the role of cognitive processes, the influence of other

emotions than fear (e.g. anger or shame); and abnormalities in memory (fragmented declarative memory, some reexperiencing symptoms which may not be explained by conditioning like nightmares or some intrusive memories as flashbacks (Brewin & Holmes, 2003). However, the conditioning approach gives an important treatment rationale (exposure). Furthermore, the basic assumptions of the model have been integrated in newer cognitive-behavioral models of PTSD (Ehlers & Clark, 2000; Foa & Kozak, 1986).

Emotional Processing theory

Foa and colleagues (Foa & Kozak, 1986; Foa, Steketee, & Rothbaum, 1989) proposed a model of fear memory in which frightening events are represented as interconnections between nodes in an associative memory network. Based on Lang's (1979) conceptualizations of fear they proposed that traumatic fear memory includes three kinds of information: (a) information about the feared stimuli situation (e.g. sounds or visual stimuli) (b) information about the persons response (physiologic, behavioral, emotional, verbal), and (c) meaning information about the stimulus (e.g. danger) and response elements of the structure. Foa et al. stress the great significance of the traumatic event and the violation of formerly held basic concepts of safety which distinguishes PTSD from other anxiety disorders. The model integrates stimulus, response and meaning/cognition propositions. These elements are activated and strongly associated during the traumatic event. The resulting fear memory structure in PTSD patients (in contrast to simple phobics) is characterized by: (a) the size of the structure: a large number of environmental stimuli may activate the structure (e.g. cars, streets, darkness, noise) (b) the high intensity of responses both physiological and behavioral, and (c) the low threshold for activation of the fear structure. The more elements are integrated in fear structure the more often it may be activated due to internal or external cues and the more severe the PTSD symptoms may be. In response to reminders of the traumatic event the entire fear memory will be retrieved.

Foa and colleagues (e.g. Foa & Rothbaum, 1998) elaborated their theory by incorporating several cognitive elements: prior to trauma extreme rigid positive or negative views about the self and the world might be risk factors for PTSD. Furthermore, negative cognitive schemas involving danger and incompetence, that are hypothesized to underlie chronic PTSD, may be reinforced by negative appraisals of later PTSD symptoms, events during the trauma, and reactions of others or disruption in daily activities.

Based on the theory Foa et. al. suggested a highly successful treatment intervention, prolonged exposure (see also chapter 2.7). In order to reduce the strong associations between the elements of the structure, the complete fear structure needs to be activated and modified by incorporating fear-incompatible information. The experience of habituation of fear (within and between therapy sessions) due to exposure (e.g. in vivo or in sensu) is thought to weaken the association between the feared situation and other elements (e.g. emotional/ physiological responses and its meaning) of the fear structure (Foa et al., 1989). Foa and Rothbaum (1998) summarized possible working mechanisms for exposure: (a) it prevents avoidance and thus reinforcement of fear memory, (b) it allows change in negative cognitive interpretations and incorporation information about safety into the fear structure, (c) it allows discrimination from other events, (d) offers the possibility of mastery during exposure (e) allows integration of the trauma memory in the autobiographical memory.

The theory has great explanatory power and has been empirically supported (see reviews Foa, 1997; Hembree & Foa, 2000). However, it has been criticized for several reasons. The hypothesized mechanisms of change due to exposure (e.g. habituation, change in the structure of trauma memories, and initial activation of fear) have not consistently found to predict treatment outcome (e.g. van Minnen & Foa, 2006; van Minnen & Hagedaars, 2002). Furthermore, it is not readily answered how trauma memory is altered due to exposure: incorporation of new information, conscious reappraisal of beliefs, or inhibition of old memories by new ones (for review see Brewin, 2001; Brewin & Holmes, 2003). Additionally, the conceptualization of only one network memory system is limited to explain certain features of PTSD as the fragmented trauma memories and the vivid and uncontrollable reexperiencing in the present, which is different from normal autobiographical memory (for critical discussion see Brewin & Holmes, 2003). Additionally, the role of some appraisals and cognitive/behavioral coping strategies has not been answered.

The cognitive model of Ehlers and Clark

Ehlers and Clark (2000) introduced a cognitive model of PTSD which represents an integration of prior psychological theories on cognition, learning, and memory in PTSD with some new aspects (Ehlers & Clark, 2000). The central assumption of the model is that persons with persistent PTSD process the traumatic event and/or its sequelae in a way that produces a sense of *current threat*, either an external threat (e.g. the world is unsafe) or internal threat to the self or the personal future. This sense of current threat is accompanied with PTSD

symptoms of reexperiencing (e.g. intrusions), emotional responses (e.g. anxiety, anger), and increased arousal. Ehlers and Clark (2000) proposed two major processes that lead to the sense of current threat: (1) negative appraisal of the trauma and/or its sequelae and (2) the nature of trauma memories and its link to other autobiographical memories. Furthermore, in order to cope with perceived threat and distress the individual might produce certain behavioral and cognitive processes intended to reduce the distress in a short term. This however, prevents change in appraisals and memories and thus maintains the disorder. Risk factors like *characteristics of the trauma* (e.g. severity, duration), *previous experience of trauma* or *prior beliefs* may influence these three processes, which are described as followed.

(1) *negative appraisal of the trauma and/or its sequelae*. Negative appraisals and interpretations might be focused on the: (1) traumatic event (e.g. overgeneralization of danger, appraisals of the person's reactions and behaviors during the trauma), (2) initial PTSD symptoms, (3) reactions of other people after the trauma, and (4) other negative consequences of the trauma (e.g. physical or professional/financial consequences). These appraisals may explain the variety of negative emotions (e.g. anger, guilt, shame, depression, anxiety) reported by PTSD patients. Furthermore, negative appraisals are hypothesized to encourage the individual to engage in dysfunctional coping strategies (e.g. avoidance) and may influence retrieval and elaboration of trauma memories.

(2) *The nature of traumatic memory*. Patients have difficulties in intentionally retrieving a complete memory of the traumatic event and this intentional recall is fragmented (e.g. missing details) and disorganized (e.g. exact temporal order of events). On the other hand reexperiencing symptoms are usually (a) very vivid brief sensory impressions of the traumatic experience (mostly visual but also bodily sensations, sounds, smells, and tastes), (b) lacking a time perspective ('here and now' quality), (c) as well as context variables (isolated and disconnected from what happened before and afterwards) (d) characterized by affect without recollection (reexperiencing of emotions or physiological sensations without recollection about the traumatic event), and (e) easily triggered by a wide range of trauma-related external cues (e.g. physical cues similar to those present during the trauma like certain visual or auditory cues) or internal cues (e.g. emotional states, body sensations) (Ehlers & Clark, 2000; Ehlers et al., 2004).

Ehlers and Clark (2000) proposed that autobiographical memory for trauma is not sufficiently elaborated and integrated with other information (e.g. time, place, subsequent and previous information) and other parts of autobiographical memories. This explains (a)

problematic intentional recall, (b) poor inhibition of unintentional memories, and (c) retrieval without context. Two basic learning mechanisms are suggested to lead to easy triggering of memories and emotions by associated stimuli: (1) strong associative learning: strong S-S and S-R associations for traumatic material; (2) strong perceptual priming (a form of implicit memory) for stimuli associated with the traumatic event which leads to a reduced perceptual threshold for these stimuli and a poor stimulus discrimination (Ehlers & Clark, 2000; Ehlers et al., 2004).

(3) *Dysfunctional coping strategies intended to control threat and PTSD symptoms.* Ehlers and Clark (2000) identified a large number of maladaptive behavioral and cognitive strategies that are thought to maintain PTSD in three ways by: (1) directly producing PTSD symptoms, (2) preventing change in negative appraisal of the trauma and its sequelae, and (3) preventing change in trauma memories. Among the *behavioral* strategies are: avoidance of trauma reminders (e.g. similar situations), avoidance to talk about the trauma, distraction, safety seeking behaviors, the use of alcohol or medication to control anxiety, giving up of normal activities (e.g. sport, hobbies). Maladaptive *cognitive* strategies include: avoidance to think about the trauma, rumination, selective attention to threat cues, dissociation, or thought suppression.

Ehlers and Clark (2000) integrated findings from risk-factor research into their model. They suggested that *peritraumatic cognitive processing* may influence development of negative appraisals and trauma memory. Among them ‘mental defeat’ (the perceived loss of psychological autonomy and feeling of no longer being a human) may be a risk factor for negative self appraisals. Furthermore, trauma memory might be influenced by peritraumatic processing like: dissociation during trauma (e.g. depersonalization, derealization, emotional numbing), a lack of so called conceptual processing (vs. data-driven processing), a lack of cognitive capacity, or the inability to establish a self referral perspective while experiencing the trauma.

There is good evidence supporting the various aspects of the model (for reviews see Brewin & Holmes, 2003; Ehlers & Clark, 2000; Ehlers et al., 2004). Especially, variables such as cognitive processing during trauma, memory disorganization, negative appraisals of trauma and sequelae, safety behaviors, rumination, thought suppression, and dissociation have been found to predict maintenance and severity of PTSD in prospective studies even after controlling for initial symptoms and event characteristics (Dunmore, Clark, & Ehlers, 2001; Ehlers, Mayou et al., 1998; Ehlers, Mayou, & Bryant, 2003; Ehling, Ehlers, & Glucksman,

2006; Ehring et al., 2008; Halligan, Michael, Clark, & Ehlers, 2003; Kleim & Ehlers, 2008; Mayou et al., 2002), although there are also contradictory results (e.g. Field, Norman, & Barton, 2008; Halligan, Clark, & Ehlers, 2002). Especially the distinction between data-driven versus conceptual processing during trauma and the measurement via retrospective self-report has been questioned (Brewin & Holmes, 2003).

In summary, the model has great explanatory power explaining different typical abnormalities in memory, emotion, cognition, and behavior of PTSD patients. Furthermore, the model gives a clear rationale for treatment of PTSD (see also treatment section) suggesting a need for change in the three key features of their model: trauma memory, negative appraisals, and dysfunctional cognitive/behavioral strategies and thus represents an extension to only exposure therapies (Ehlers & Clark, 2008).

2.5.3 Dual representation theory

Brewin and colleagues (Brewin, 2001, 2008; Brewin, Dalgleish, & Joseph, 1996; Brewin & Holmes, 2003) suggested that there are two distinct memory systems in order to explain certain phenomena of PTSD like disorganization of trauma memory, reexperiencing in kind of spontaneous vivid flashbacks, and the time distortion and unpredictability of intrusive memories. According to the dual representation theory traumatic events can be stored in two different representational formats: the verbally accessible memory (VAM) and the situational accessible memory (SAM). The VAM supports ordinary autobiographical memory that can be deliberately retrieved and may interact with the rest of the autobiographical knowledge. The VAM contains information that the individual has consciously attended before, during, and after the traumatic event and is integrated within the personal context comprising past, present, and future. Furthermore, the VAM contains conscious evaluations and appraisals of the trauma both at the time it was happening and afterwards (consequences and implications of the event). Thus, the VAM memories are associated with primary emotions (experienced during the traumatic event) and secondary emotions generated by cognitive appraisals.

The second type of memory the SAM contains information from lower level perceptual processing of the traumatic event (e.g. visuospatial information) which did not receive much conscious attention. The SAM stores also the person's bodily responses to it (e.g. autonomic, motor, and emotional) as well as the primary emotions that were experienced during the trauma (e.g. fear, horror, or helplessness). The SAM does not use verbal code and therefore does not necessarily interact with other autobiographical memories. Flashbacks are

thought to reflect operation of the SAM. These memories are difficult to control because they are involuntarily triggered by reminders of the traumatic event which can be external cues (e.g. smells, sounds, or sights) or internal mental processes. Furthermore, the operation of the SAM explains why flashbacks are more detailed and emotionally laden than ordinary memories.

Brewin (2001, 2008) related his theory to findings from cognitive neurosciences. He suggested that the VAM is dependent on the activity of the hippocampus, because hippocampus-dependent pathways result in an integrated, coherent representation of conscious experience, located in an appropriate temporal and spatial context. He proposed that degeneration of the hippocampus, as observed in PTSD patients, may impair functioning of the VAM. In contrast, the SAM memories which are highly perceptual, experienced as happening in the present, and elicited automatically seem to be associated with amygdala activation that appears to be enhanced with increased stress.

Brewin (Brewin, 2001, 2006) suggested that two processes are necessary to treat resulting PTSD symptoms. He recommended that deliberately focusing on the content of flashbacks or hot spots (as during prolonged exposure in sensu) may promote recoding of information of the SAM into the VAM system, where this information is integrated into a spatial and temporal context. When a person is then exposed to trauma reminders there will be a retrieval competition between VAM and SAM systems. If the new VAM memories are accessible, inhibitory influences from the prefrontal cortex may prevent inappropriate amygdala activation.

In a second process, a change within the VAM system may occur. Negative beliefs about the self, the world, or the future stored in the VAM may be challenged by the creation of alternative and more appropriate representations in memory (e.g. due to cognitive therapy) that are preferentially retrieved. Again, using the principle of retrieval competition old representations and cognitions remain unchanged but are challenged by new ones (Dudai, 2006). These old cognitions however retain their potential of being retrieved. In this view, the theory accounts also for effectiveness of treatments like imagery rescripting.

There is some empirical evidence for the predictions of two types of memory in normal subjects (Brewin, 2007 for review; Brewin & Saunders, 2001; Holmes, Brewin, & Hennessy, 2004) and PTSD patients (Hellowell & Brewin, 2002). However, more research is necessary to support the assumptions. Furthermore, the model tries to explain certain features of PTSD (the role of memory, emotions, and appraisals) but leaves others out (e.g. the role of

behavioural strategies, dissociation). The model does have several implications for therapy, but a detailed outline of therapeutic procedures has not been given. Probably the most important account of the model is the link between cognitive psychology and cognitive neuroscience (see also chapter 2.6) findings in PTSD research.

3.5.4 Summary

Clearly there is a great overlap between the psychological models of PTSD reviewed here. For example the ideas of the conditioning model (classical and operant conditioning) have to some extent been incorporated in all newer theories. The three recent models reviewed here added some important aspects to the understanding of PTSD such as the role of: (1) memory (encoding and alterations in memory functioning); (2) appraisals and prior beliefs; and (3) cognitive and behavioral coping strategies. Furthermore they (to a lesser extent the Brewin model) provided powerful treatment possibilities (see also chapter 2.7). The greatest difference between the models are: (1) how trauma influences memory, although there is some overlap between the Ehlers and Clark and the Brewin model which both postulate two different memory systems; (2) the interaction between appraisal, memory and coping strategies, here the Ehlers model clearly provides the most explanations; (3) elaboration of trauma memory by imaginal exposure: here the Brewin model differs (based on neuroscience research) by proposing that reliving of the trauma leads to new instead of reintegrated memories, which compete with the original representations. In summary, all theories make unique contributions for the understanding of psychological processes underlying the development and maintenance of the complex disorder PTSD (for an extended discussion please see Brewin & Holmes, 2003). By now, the model by Ehlers and Clark probably offers the most detailed explanation of different aspects on cognitive, behavioral and emotional disturbances of the disorder. However, the Brewin model shows a link between psychological and neurobiological research of PTSD, which might be very inspiring for each other.

2.6 Neurobiological aspects of PTSD

Psychobiological symptoms (e.g. startle reaction, increased physiological reactivity to traumatic stressors) are core symptoms of PTSD. Furthermore, PTSD has been conceptualized as reaction to stress. This has led to examination of biological parameters trying to explain genesis and course of specific cognitive, emotional, and behavioral abnormalities observed in

PTSD. Biological dysregulations associated with PTSD can be measured on neurohormonal, immunologic, physiologic and (functional) neuroanatomical levels. There is evidence of alterations in many biological systems: e.g. the hypothalamic–pituitary–adrenal (HPA) axis, monoamine transmitters (noradrenaline, dopamine, serotonin), the neuropeptide system, other neurotransmitters, as well as neuroimmunological alterations which are reviewed elsewhere (Hageman, Andersen, & Jorgensen, 2001; Heim & Nemeroff, 2009; Vermetten & Bremner, 2002). Furthermore, there is extant evidence for elevated psychophysiology in PTSD (see reviews Buckley & Kaloupek, 2001; Orr, Metzger, & Pitman, 2002; Pole, 2007). Because of major interest for the current thesis, the following chapter will focus on a summary of the current knowledge about structural and functional neuroimaging findings of PTSD as well as studies that investigated treatment related changes of brain structure and function in PTSD subjects.

2.6.1 Neuroimaging findings in PTSD

During the last decade, PTSD has been studied using different neuroimaging techniques such as magnetic resonance imaging (MRI), proton magnetic resonance spectroscopy (MRS), functional MRI (fMRI), positron emission tomography (PET), and single-photon emission computed tomography (SPECT). These studies provide information about structural and functional abnormalities in PTSD that might underlie pathogenesis and symptoms of PTSD. However, the results of these studies are far from uniform (for excellent reviews, see Bremner, 2007; Francati, Vermetten, & Bremner, 2007; Hull, 2002; Jatzko, Schmitt, Kordon, & Braus, 2005; Karl et al., 2006; Liberzon & Sripada, 2008; Villarreal & King, 2001). Neuroimaging studies in PTSD have suggested a number of brain regions meriting further attention. Replicated regional abnormalities have been found in the hippocampus, amygdala, medial prefrontal cortex (mPFC), and Broca's Area.

Hippocampus. Most studies of structural brain abnormalities in PTSD have especially focused on the hippocampus although other structural abnormalities have been reported (for meta-analytic review see Karl et al., 2006). The hippocampus is critically involved in the control of stress responses, explicit (declarative) memory, working memory and autobiographical memory. Chronic stress may affect the hippocampus through elevated levels of glucocorticoids released during stress, stress-related inhibition of brain-derived neurotrophic factor (BDNF), changes in serotonergic function, or inhibition of neurogenesis in the hippocampus (see reviews Bremner, 1999, 2006b; Sapolsky, 1996). Patients with PTSD

have been shown to have deficits in hippocampal-based memory (Bremner, 2006a). The most replicated structural finding is hippocampal volume reduction (see meta-analyses Karl et al., 2006; Kitayama, Vaccarino, Kutner, Weiss, & Bremner, 2005; Smith, 2005; Woon & Hedges, 2008). Many studies found reduced hippocampal volumes (e.g. Bonne et al., 2008; Bremner et al., 1997; Bremner, Vythilingam, Vermetten, Southwick, McGlashan, Nazeer et al., 2003; Gurvits et al., 1996; Stein, Koverola, Hanna, Torchia, & McClarty, 1997; Villarreal et al., 2002) whereas others do not (e.g. Jatzko et al., 2006; Pederson et al., 2004; Schuff et al., 2001). These differences might in part be explained by moderator variables such as MRI methodology, PTSD severity, comorbidity, medication, age, and gender (Karl et al., 2006; Pitman, 2001; Vythilingam et al., 2005).

A study using monozygotic twin pairs questioned whether reduced hippocampal volumes are a consequence of traumatic experience (Gilbertson et al., 2002). Although they found that PTSD severity in PTSD patients who were exposed to trauma was negatively correlated with the hippocampal volume, smaller hippocampi were also found in the unexposed twin of patients with severe PTSD. Gilbertson and associates concluded that smaller hippocampal volume might be a premorbid risk factor for development of PTSD, rather than a consequence of PTSD or trauma exposure. However, the study did not control for prior trauma and socioeconomic status. Furthermore, preliminary evidence suggests that there might be no hippocampal volume reduction in the first time post trauma. Two longitudinal studies with up to a 2-year follow-up period have found no difference between PTSD and non-PTSD subjects in hippocampal volumes or volume reduction over time (Bonne et al., 2001; De Bellis, Hall, Boring, Frustaci, & Moritz, 2001). However, it can not be concluded from these studies whether smaller hippocampal volume might occur in individuals chronic or complicated PTSD.

Studies using MRS have shown a reduction of the brain metabolite N-acetyl aspartate (NAA), which is a very sensitive measure of neuronal integrity (e.g. Schuff et al., 1997; Schuff et al., 2001). These findings have been interpreted as evidence for metabolic changes in the hippocampus, more sensitive to neuronal damage in PTSD than volume loss (Schuff et al., 2006). Further, studies using functional neuroimaging have revealed deficits in hippocampal activation during cognitive activation paradigms (e.g. memory tasks) in subjects with PTSD (Astur et al., 2006; Bremner, Vythilingam, Vermetten, Southwick, McGlashan, Nazeer et al., 2003; Bremner, Vythilingam, Vermetten, Southwick, McGlashan, Staib et al., 2003; Werner et al., 2009).

Amygdala. There is also evidence for structural alterations of the amygdala in individuals with PTSD, although effect sizes are rather small and attenuated relative to hippocampal volume reductions (Karl et al., 2006). Furthermore, alterations in amygdala function have been reported. Functional neuroimaging studies in PTSD include symptom provocation paradigms (e.g. script-driven imagery, trauma-relevant sounds or pictures), cognitive activation paradigms, or administration of anxiogenic pharmacologic agents (Liberzon & Martis, 2006). Amygdala hyperresponsivity has been reported for PTSD patients during presentation of trauma-related stimuli (e.g. Liberzon et al., 1999; Pissiota et al., 2002; Rauch et al., 1996; Shin, McNally et al., 1997; Shin, Orr et al., 2004) as well as for trauma-unrelated affective or neutral materials (e.g. Rauch et al., 2000; Semple et al., 2000; Shin et al., 2005). However, several functional neuroimaging studies have failed to find any amygdala activation during symptomatic states in PTSD (e.g. Bremner et al., 1999; Lanius et al., 2001; Shin et al., 1999).

The amygdala is regarded a central structure in the emotional network of the brain and has connections to cortical and subcortical regions. It is involved in the assessment of threat-related stimuli, emotional responses, and is necessary for the process of fear conditioning (Davidson, 2002; LeDoux, 2000, 2003). Accordingly, PTSD patients show relatively heightened acquisition of conditioned fear in the laboratory (Orr et al., 2000; Peri, Ben-Shakhar, Orr, & Shalev, 2000) and increased activation of the amygdala during fear acquisition (Bremner, Vermetten et al., 2005; Doronbekov et al., 2005).

Medial prefrontal cortex. Functional neuroimaging studies have found a relatively diminished responsivity in medial prefrontal cortex (mPFC), including the orbitofrontal cortex, anterior cingulate cortex (ACC), subcallosal gyrus, and medial frontal gyrus in PTSD (e.g. Bremner, Vermetten et al., 2005; Lanius et al., 2001; Lindauer et al., 2004; Shin et al., 1999; Shin, Orr et al., 2004; Shin et al., 2001; Shin et al., 2005). However, there are also discrepant results e.g. of increased activation (e.g. Shin, Kosslyn et al., 1997; Zubieta et al., 1999). Additionally, several recent morphometric MRI studies have reported decreased volumes of the medial prefrontal cortex (e.g. Rauch et al., 2003; Woodward et al., 2006; Yamasue et al., 2003). The mPFC has inhibitory connections to the amygdala (Ghashghaei & Barbas, 2002; Grace & Rosenkranz, 2002) where it exerts control over stress responses and emotional reactivity. Furthermore, it is involved in the process of extinction of fear conditioning (Milad & Quirk, 2002; Morgan, Romanski, & LeDoux, 1993; Quirk, Garcia, & Gonzalez-Lima, 2006; Quirk, Russo, Barron, & Lebron, 2000). Thus, it has been

hypothesized to be part of a circuit involved in the fear response in PTSD. Recent studies with PTSD patients showed impaired extinction of fear in the laboratory (Blechert, Michael, Vriends, Margraf, & Wilhelm, 2007; Wessa & Flor, 2007) and involvement of the mPFC in the process of fear extinction (Milad et al., 2009).

Broca's area. Another impairment in a brain region implicated by functional neuroimaging studies is decreased activation of left-hemisphere Broca's area (e.g. Rauch et al., 1996; Shin, Kosslyn et al., 1997), a brain structure responsible for speech production. This could be an explanation for difficulties of PTSD patients to verbalize their traumatic experiences. Other brain regions that have been implicated in PTSD are insula, thalamus, posterior cingulate, parietal and visual cortex (e.g. Hull, 2002; Jatzko et al., 2005; Liberzon & Sripada, 2008).

Hemispheric differences. There is some evidence for hemispheric differences in functional imaging studies with a favor for enhanced right hemisphere activation of several brain regions during processing of negative stimuli in PTSD subjects (Bremner et al., 1999; Rauch, Savage, Alpert, Fischman, & Jenike, 1997; Rauch et al., 1996). However, there is only one neuroimaging study that directly investigated hemispheric asymmetry in individuals with PTSD. They found support for the assumption of enhanced right hemisphere involvement in PTSD (Pagani et al., 2005). Furthermore, support of enhanced right hemisphere involvement in PTSD comes from a study investigating regional lesions in injury survivors (Herskovits, Gerring, Davatzikos, & Bryan, 2002). Subjects with PTSD reexperiencing symptoms had fewer limbic lesions on the right, which has been interpreted as evidence for dependence of PTSD reexperiencing on right hemisphere functioning. A study using functional connectivity analysis of brain activity (fMRI) during recall of traumatic memories found greater correlation of brain activity in right hemisphere regions as compared to traumatized healthy controls who showed an opposite pattern of greater left hemisphere interregional correlations (Lanius et al., 2004). These differences in brain connectivity have been interpreted as evidence for the nonverbal nature of traumatic memory recall in PTSD subjects, compared to a more verbal pattern of traumatic memory recall in comparison subjects. There are three studies investigating electroencephalographic (EEG) asymmetries in PTSD. One study reported right-sided activation in response to trauma-related olfactory stimuli in a small sample (n = 5) of Vietnam veterans with PTSD (McCaffrey, Lorig, Pendrey, McCutcheon, & Garrett, 1993). Metzger et al. (2004) reported that PTSD arousal symptoms were associated with increased relative right parietal baseline activity in a sample of female Vietnam War

nurse veterans. However, recently Shankman et al. (2008) did not find any differences in brain asymmetry during rest in a sample of PTSD subjects with mixed trauma as compared to a control group.

A neurocircuitry model of PTSD

Given the findings of reduced hippocampal volume, increased amygdala activation, and decreased activation of the medial prefrontal cortex current neurocircuitry models of PTSD (Brewin, 2008; Cannistraro & Rauch, 2003; Elzinga & Bremner, 2002; Rauch, Shin, & Phelps, 2006; Shin, Rauch, & Pitman, 2006; Villarreal & King, 2001) posited that: (1) a lower threshold to activate the amygdala leads to increased fear conditioning; (2) a dysfunctional MPF, a structure that normally inhibits the amygdala, may further enhance the effects of the amygdala and lead to failure to extinction, thereby increasing the frequency and emotional intensity of traumatic memories; (3) hippocampal dysfunction may be a consequence of chronic hyperarousal and partly account for the memory dysfunctions (i.e. declarative) in PTSD patients. Furthermore, connections between amygdala and hippocampus are implicated in context conditioning. Especially hippocampus and amygdala have been proposed to represent the neural substrate for trauma memories in PTSD (Brewin, 2001, 2008).

Methodological issues and limitations of current neuroimaging research in PTSD

Taken together replicated findings of brain imaging studies show a dysfunction of several brain regions that may be involved in emotional and cognitive disturbances of PTSD. However, the results are far from uniform. Reasons for this might be methodological differences of the studies regarding: (1) imaging techniques (e. g. neuroimaging method, image acquisition and analysis), (2) experimental procedures (e.g. type of symptom provocation stimulus: generalized versus personalized), (3) PTSD samples (combat veterans [mostly male], victims of childhood physical and sexual abuse [mostly female]), (4) different chronicity of PTSD, (5) differences in inclusion criteria (substance abuse, medication); (6) psychiatric comorbidity, (7) PTSD severity and diagnosis. This makes it difficult to compare results of different studies (Hull, 2002; Jatzko et al., 2005; Kemp et al., 2007; Lanius et al., 2007). Further, especially for PTSD, there is a great inter individual variability of cognitive-emotional responses to traumatic events (for review see Lanius, Bluhm, Lanius, & Pain, 2006; Lanius, Hopper, & Menon, 2003), which is likely to account for many of the inconsistencies in previous work. Another point is that brain alterations often do not correlate with either

symptom severity or neuropsychological functioning (e.g. smaller hippocampus not related to memory deficits) which impairs interpretability of the results. Furthermore, as stated by Liberzon and Marti (2006) neuroimaging findings do not readily explain the complex phenomenology of PTSD and other possible relevant mechanisms that may underlie development and persistence of PTSD such as: stimulus generalization, intrusive memories, resilience, cognitive–emotional modulation (appraisal and reappraisal), social and self-related emotional processing, and habituation. Therefore, a link of neuroimaging findings and research to current psychological models might be necessary.

Generally, there are great expectations what neurobiological research can further the understanding of the pathophysiology of PTSD. For example, in their review Nutt and Malizia (2004, p. 16) suggested that neuroimaging techniques “could be used to identify persons at high risk or to confirm the diagnosis of this disorder”. However, although there are replicated neurobiological correlates of PTSD (see above, and e.g. increased psychophysiological reactivity, dysfunction of HPA-axis) there is also a large amount of contradictory results (Rosen & Lilienfeld, 2008). Furthermore, the neurobiological correlates of PTSD are often not specific for PTSD. For example, reduced hippocampal volume has been observed in depression, alcoholism, and neurological trauma (e.g. Jelicic & Merckelbach, 2004). Also heightened physiological reactivity or amygdala activation to unpleasant emotional stimuli have been reported in other anxiety disorders (e.g. Cannistraro & Rauch, 2003; Craske & Waters, 2005; Straube, Mentzel, & Miltner, 2005). Thus, the Institute of Medicine (IOM, 2006, p.46), concluded that, “No biomarkers are clinically useful or specific in diagnosing PTSD, assessing the risk of developing it, or charting its progression”.

2.6.2 Treatment related brain changes in PTSD.

There is some preliminary evidence of alterations of brain activation and structure due to treatment (pharmacological or psychological) of PTSD.

Pharmacological treatment studies. Fernandez et al. (2001) found a normalization of PET activation in response to trauma-related sounds in prefrontal and paralimbic cortices after SSRI (fluoxetine) administration in one PTSD patient. Another study, using SPECT during baseline, found changes in brain activation in temporal and prefrontal cortical areas after treatment of 11 PTSD patients treated with SSRI citalopram (Seedat et al., 2004). Two structural MRI studies showed that both, hippocampal atrophy and hippocampal-based memory deficits reversed with treatment with the SSRI paroxetine in 20 PTSD patients

(Vermetten, Vythilingam, Southwick, Charney, & Bremner, 2003), and with the anticonvulsant phenytoin in 11 PTSD patients (Bremner, Mletzko et al., 2005).

Psychological treatment studies. There are only few studies that investigated changes in brain structure and activity due to psychological treatment for PTSD. In a structural MRI study Lindauer et al. (2005) did not find volume changes in hippocampus due to brief eclectic psychotherapy in 8 PTSD subjects. However, Bossini et al. (2007) found an increase in bilateral hippocampus volume in one subject with PTSD after 8 weeks of Eye Movement Desensitization and Reprocessing (EMDR).

Some studies reported changes in brain *function* due to EMDR treatment. Levin, Lazrove, and van der Kolk, (1999) reported an increased activation of the anterior cingulate gyrus and the left frontal lobe after successful treatment of one PTSD patient with EMDR. Lansing, Amen, Hanks, and Rudy (2005) found, after successful EMDR treatment of six police officers with PTSD, decreased activity using SPECT (in response to a concentration task) in the left and right occipital lobe, left parietal lobe, and right precentral frontal lobe as well as significant increased perfusion in the left inferior frontal gyrus. Pagani et al. (2007) reported increased activity in temporal cortex and thalamus and normalization of parahippocampal activation after EMDR treatment in 15 PTSD patients using SPECT during script-driven symptom provocation.

Lindauer et al. (2008) investigated the effect of brief eclectic therapy in 20 civilian PTSD out-patients (randomly assigned to a treatment and a wait-list condition) using SPECT during trauma script-driven imagery. Before treatment they found greater activation in the right insula and right superior/middle frontal gyrus in the PTSD group as compared to 15 traumatized control subjects. After treatment they found lower activation in the right middle frontal gyrus in the treatment group, compared to the waiting list. Furthermore, they found that symptom reduction was related to increase in activation in left superior temporal gyrus, and superior/middle frontal regions.

There are few studies investigation functional changes of brain due to *cognitive behavioral therapy* (CBT). Felmingham et al. (2007) reported after CBT increased ACC and reduced amygdala activation measured via fMRI during viewing fearful facial expressions 5 PTSD participants. However, no control group was tested. Farrow et al. (2005) investigated 13 patients with civilian traumas using fMRI in social-cognition tasks. Post-therapy they found middle temporal gyrus activation in response to empathy judgments and posterior cingulate gyrus activation in response to forgivability judgments. They propose that these

regions may be responsible for these social-cognitive judgments in healthy subjects. However, they did not include comparison groups. Two recent studies of Bryant and coworkers showed that activation of the amygdala and ACC (Bryant, Felmingham, Kemp et al., 2008) as well as volume of the ACC (Bryant, Felmingham, Whitford et al., 2008) predicted treatment response to CBT in mixed trauma samples with PTSD (n=14, 13, respectively).

Of special interest is the study of Peres et al. (2007), which evaluated changes in cerebral blood flow using SPECT during a script-driven symptom provocation paradigm in 16 subsyndromal PTSD patients as compared to a waitlist group (11 subsyndromal PTSD). After successful CBT treatment they found higher activity in parietal lobes, left hippocampus, thalamus and left prefrontal cortex in PTSD patients as compared to the waitlist group. However, they did not evaluate pre-post changes between the two groups. The authors interpreted their findings as being partly in line with a recent psychological model proposing that successful cognitive behavioral treatment leads to a more integrated verbally-accessible memory of the traumatic event (Brewin, 2001, 2008).

Summary

In summary, there is some evidence of treatment related changes in brain activation and structure. Pharmacological studies demonstrated an increase in hippocampal volume, consistent with the view that there is plasticity in brain networks associated with PTSD (Bremner, Elzinga, Schmahl, & Vermetten, 2008), although these studies did not include control groups. However, psychological treatment did not produce hippocampal volume changes in PTSD subjects (Lindauer et al., 2005). Functional neuroimaging studies showed treatment related changes in diverse subcortical and cortical brain regions that have been associated with PTSD symptoms. However, care must be taken in interpretation of the results since almost all of these treatment studies (pharmacological and psychological) are nonexperimental pretest/posttest comparison without control groups or have other methodological limitations (e.g. patients receiving concomitant pharmacotherapy). Thus, there was no control of confounding factors: e.g. treatment-specific changes (differences to control or waitlist groups); or the effect of repeated measures (e.g. reactivity of measurement, habituation). Furthermore, the great methodological heterogeneity of the studies (e.g. imaging techniques; experimental procedures; PTSD samples and severity) makes it hard to compare findings of different studies.

2.7 Treatment of PTSD

There is a great number of studies providing strong support for the efficacy of psychological therapy for PTSD (see reviews Bradley, Greene, Russ, Dutra, & Westen, 2005; Foa, 2006; Foa, Keane, & Friedman, 2000; Hembree & Foa, 2000; Mendes, Mello, Ventura, Passarela Cde, & Mari Jde, 2008; Sherman, 1998; Van Etten & Taylor, 1998). Cognitive behavioral therapy (CBT) such as exposure therapy, cognitive therapy, and anxiety management techniques (for description see below) are treatments that have the greatest empirical support in efficacy studies across diverse trauma populations. Evidence also supports the efficacy of Eye Movement Desensitization and Reprocessing (EMDR) which has been developed by Shapiro (Shapiro, 1995). In EMDR patients are encouraged to imagine a stressful scene and replace dysfunctional cognitions with more adaptive ones while engaging in lateral eye movements. However, findings about efficiency of EMDR vary across studies and evidence suggests that the eye movements, integral to the treatment and to its name, might be not necessary (for discussion see Davidson & Parker, 2001.; Keane et al., 2006). Furthermore, it has been criticized that EMDR lacks of a convincing theoretical model and thus a specification of the mechanisms of change (Davidson & Parker, 2001). Regarding pharmacological treatments for PTSD there is a range of medications used for treating the disorder. The strongest evidence to date is for antidepressant medications, particularly selective serotonin reuptake inhibitors (SSRIs) (Davidson, 2006; Friedman, Davidson, Mellman, & Southwick, 2000; Stein, Ipser, & Seedat, 2006; Van Etten & Taylor, 1998). However, the effect size for SSRIs even in the largest clinical trials is mostly smaller than those of psychological treatments for PTSD, and there are serious problems with long-term-effectiveness, and a high rate of discontinuation of treatment in medication trials. Thus, psychological treatments should be the treatment of choice (for reviews see Keane et al., 2006; Van Etten & Taylor, 1998). Because of special relevance for this thesis CBT approaches, which are based on psychological theories of PTSD (see chapter 2.5), will be described here.

2.7.1 Cognitive behavioral therapy of PTSD

Exposure therapies

Exposure therapy includes confrontation (a) of memories (in sensu) of the trauma or (b) cues/triggers (in vivo) related to the traumatic event. *In sensu exposure* is applied using

imaginal forms of exposure. During prolonged imaginal exposure (PE) (Foa, 2006; Foa & Rothbaum, 1998; Foa et al., 1989) the patient is required to vividly imagine the trauma for prolonged periods. The therapist assists the patient to provide a narrative of their traumatic experience in a way that emphasizes all relevant details, including sensory cues and affective responses. In an attempt to maximize the sense of reliving the experience, the individual may be asked to provide the narrative in the present tense, speak in the first person, and ensure that there is focus on the most distressing aspects (hot spots). Other variants of imaginal exposure involve requiring clients to repeatedly write down detailed descriptions of the traumatic event (Blanchard et al., 2003; Resick & Schnicke, 1993). *In vivo exposure* generally involves returning to the site of the traumatic event and in the case of MVAs driving.

There is considerable debate concerning the change mechanisms of exposure (Foa & Rothbaum, 1998; Rothbaum & Schwartz, 2002). It is suggested that exposure promotes: (1) habituation and therefore reduces anxiety, (2) correction of dysfunctional beliefs, (2) the feeling of mastery, (4) incorporation of corrective information into autobiographical trauma memory, and impedes negative reinforcement due to avoidance. There is extant evidence that exposure is highly effective in reducing PTSD symptoms. Furthermore, exposure alone seems to be equally effective as cognitive therapy (CT) or combined CBT protocols (for reviews see Bradley et al., 2005; Foa et al., 2005; Mendes et al., 2008).

Cognitive therapy

Psychological treatment models proposed that resolution of PTSD requires the change of negative appraisals (Ehlers & Clark, 2000) or the integration of corrective information that is incompatible with the existing fear structures (e.g. Foa et al., 1989). Cognitive restructuring involves teaching patients to identify and evaluate negative automatic thoughts, appraisals, and beliefs about the trauma, the self, the world, and the future (Ehlers, 1999; Ehlers & Clark, 2000; Ehlers, Clark, Hackmann, McManus, & Fennell, 2005; Marks, Lovell, Noshirvani, Livanou, & Thrasher, 1998). Resick and Schnicke (1993) have proposed cognitive processing therapy (CPT) involving five major cognitive themes (safety, trust, power, esteem, and intimacy) that are suggested to be central in traumatized individuals. There is evidence that cognitive therapies for PTSD are equally effective as exposure. Though, a combination of exposure and cognitive therapy (CBT) has not been shown superior to single use of this treatment (Van Etten & Taylor, 1998). However, as reviewed by Ehlers and Clark (2008) a cognitive-behavioral treatment protocol based on the model of Ehlers and Clark (2000), which

incorporated some new cognitive and behavioral techniques, has shown greater effect sizes and lower dropout rate than established CBT approaches. However, there is still need for independent replication of these results.

Anxiety management

Typically, anxiety management training (AMT) involves teaching patients a number of behavioral and cognitive strategies (coping skills) to enhance their capacity to manage the emotions and arousal associated with PTSD. Furthermore, skills are trained that assist the individual during exposure to the traumatic memories or situations. Anxiety management approaches often include stress inoculation training (SIT) according to Meichenbaum (1985) which includes coping skills as psychoeducation, relaxation training, breathing retraining, self-coaching dialogues, thought stopping. The goal is that patients learn to manage trauma related anxiety with confidence and efficacy. AMT has been shown effective in the treatment of PTSD and is part of many treatment protocols (Bradley et al., 2005), although alone it has been shown less effective as exposure (e.g. Foa et al., 1999).

Summary

In summary, exposure therapy, cognitive therapy, and interventions incorporating AMT components have been shown highly effective across diverse populations of trauma survivors and should be given priority in treating PTSD patients (Keane et al., 2006; Nemeroff et al., 2006; Van Etten & Taylor, 1998). However, there is an ongoing debate what part of treatment to prefer. Foa and colleagues (Foa, 2006) argued that exposure might be sufficient for treatment of PTSD, since it is not enhanced by the addition of SIT or CT. Additionally, a study by Foa and Rauch (2004) showed that exposure therapy resulted in decreases in PTSD-related cognitions and the addition of CT did not enhance this effect. However, recent research showed contradictory results (Bryant, Moulds et al., 2008; Bryant, Moulds, Guthrie, Dang, & Nixon, 2003). Further, a cognitive intervention for PTSD that incorporated elements of AMT and exposure therapy seems to be highly effective (Ehlers et al., 2005) above earlier effect sizes. The question what mechanism of change is associated with a specific treatment is tricky. For example, exposure may not only promote habituation or extinction but may also provide a possibility for rethinking previous appraisals. On the other hand, cognitive interventions may indirectly foster exposure. Clearly, there is need for research on

mechanisms that underlie success in treatment. Here, neuroscience approaches could be very helpful.

2.7.2 Dresden PTSD treatment study: The CBT program of Zoellner et al. (2005)

Development of the treatment protocol

The CBT program of Zoellner, Karl, Maercker, Hickling, and Blanchard (2005) for MVA-related PTSD was adapted from a CBT program of Blanchard and colleagues (for description see Blanchard & Hickling, 2004; Blanchard et al., 2003). The original CBT protocol by Blanchard and Hickling (2004) included a combination of CBT treatments for PTSD such as psychoeducation, exposure (reading about the trauma and exposure in vivo), cognitive restructuring, and anxiety management techniques. This protocol has been shown to be effective in treating accident-related PTSD (Blanchard et al., 2003).

We translated the CBT protocol by Blanchard and Hickling (2004) into German. Furthermore the protocol was modified and extended. Additional elements in comparison to the original program are: (1) prolonged exposure based on the approach of Foa and colleagues (Foa & Rothbaum, 1998; Foa et al., 1989), (2) extended cognitive procedures as suggested by Ehlers and colleagues (Ehlers & Clark, 2000; Ehlers et al., 2005) including the combination of cognitive therapy and exposure in-sensu, (3) cognitive and behavioral techniques for treatment of guilt and anger before in-sensu exposure, (4) speaking about posttraumatic growth. A previously completed controlled, randomized treatment trial for MVA-related PTSD and subsyndromal PTSD in which this CBT program was compared to a wait-list control condition has shown the efficacy of the modified manual (Maercker, Zoellner, Menning, Rabe, & Karl, 2006).

Description of the CBT program of Zoellner et al. (2005)

The treatment allowed the therapist a range of 8–12 weekly sessions with an expected mode of 10 (for a description of the sequence of sessions see Box 2). This was done in an effort to enhance external validity of the program. The program combined several behavioral and cognitive procedures, which are described as follows:

Psychoeducation about PTSD and rationale for treatment. The first sessions included a detailed description of PTSD symptoms, emphasizing PTSD symptoms as a normal reaction to trauma. Furthermore, a rationale for the maintenance of symptoms (e.g. role of avoidance and memory) and the elements of the treatment was given.

Relaxation training. At the end of each session progressive muscle relaxation (PMR) was practiced. There was a long version (10 separate muscle groups) and a short version (5 combined muscle groups). The relaxation training was tape recorded and used by patients for home practice. Patients were asked to practice the relaxation daily.

Exposure. Three kinds of exposure were emphasized. First, the participant was reading aloud his/her description of the MVA. The patients were asked to read it aloud at home (up to 3 times per day) and record their subjective units of distress (SUDs). The second form of exposure was prolonged exposure in sensu. It followed the standard procedure for PE described by Foa and colleagues (e.g. Foa & Rothbaum, 1998) and consisted of in-sensu imagination of worst moment(s) of the accident. The initial PE session was tape recorded. The patients had to listen to the tapes once per day and rate their SUDs. This was stopped when the patient complained of boredom in the task. The third form of exposure was in vivo exposure to: (1) fear arousing cues related to traveling by automobile, (2) accident related cues, and (3) safety seeking behaviors. An individual hierarchy of avoidance tasks and safety seeking behaviors was constructed. After that, patients were asked to expose themselves with feared situations and to stop or replace safety seeking behaviors. Involvement of spouse or a significant other person for these exercises was encouraged. In addition, patients were urged to use the newly learned relaxation skills or positive coping self-talk to counter the arousal caused by working on travel hierarchy items.

Cognitive therapy. Several cognitive procedures were used in the manual. First, self-coaching dialogues were introduced. The goal was that patients learn to manage fear and arousal during driving exercises. Second, simultaneously with the in sensu and in vivo exposure, patients were instructed to monitor thoughts and feelings. Then they were taught to identify cognitive fallacies and learned how to dispute them using the general approach of Beck and Emery (1979). Furthermore, specific accident-related cognitions as described in the Ehlers and Clark model (Ehlers & Clark, 2000) of cognitive treatment of PTSD were identified and questioned e.g. overgeneralization of danger. Third, exposure in vivo was incorporated into cognitive therapy as behavioral experiments. Fourth, special emphasis was given to identify subjective guilt and anger feelings elicited by the trauma narrative. In case of predominant feelings of guilt or anger during the first reading (session 2), extended cognitive modules were applied to address and dispute these feelings. This was done before further exposure in sensu, because these secondary emotions might reduce the efficiency of prolonged exposure (Ehlers, Clark et al., 1998; Taylor et al., 2001). Fifth, attention was paid

to existential issues and if and how one could regard oneself as positively changed or personally grown by overcoming the traumatic experience and its aftermath (Zoellner & Maercker, 2006a, 2006b). When patients mentioned positive changes as a result of coping with the trauma, the reported benefits were appreciated and attributed as the patient's personal successes.

Box 2: Session-by-Session Outline of Zoellner et al.'s CBT-Manual

<i>Session</i>	<i>Treatment Components</i>	
1	Review of symptoms and diagnosis Psychoeducation about PTSD Rationale for imaginal exposure Progressive muscle relaxation (PMR) long version (LV)	PMR LV
2	Reading (aloud) written description of the MVA Exploration of major cognitive evaluations about the MVA <i>Optional modules: treatment of anger or guilt</i>	PMR LV
3	Reading (aloud) written description of the MVA Rationale for exposure in vivo and prolonged exposure (PE) Discussion of avoidance and safety seeking behaviors	PMR LV
4	PE; Creation of avoidance hierarchy; Introduction of coping self-statements	PMR LV
5	PE; Meeting with a significant other; Discussion of avoidance hierarchy	PMR LV
6	PE (optional); Discussion of avoidance hierarchy; Cognitive restructuring Progressive muscle relaxation (PMR) short version (SV)	PMR SV
7	PE (optional); Discussion of avoidance hierarchy; Cognitive restructuring	PMR SV
8	Discussion of avoidance hierarchy; Cognitive restructuring; Exploring existential issues and changes (e.g. posttraumatic growth, social isolation, depression) due to the MVA	PMR SV
9	Discussion of avoidance hierarchy; Cognitive restructuring Interventions to address estrangement, social isolation, depression or grief (optional) PE (optional)	PMR SV
10	Discussion of avoidance hierarchy; Cognitive restructuring Review all treatment procedures Relapse prevention	PMR SV

PE = Prolonged Exposure; PMR = Progressive Muscle Relaxation; SV = Short Version; LV = Long Version

2.8. Posttraumatic growth

2.8.1 Definition and description of posttraumatic growth

The understanding that suffering and distress can also be a source of positive change has existed for thousands of years and has been described in philosophy and religion (Tedeschi & Calhoun, 1995). In the past 30 years there has been extensive empirical research on negative sequelae of traumatic events like PTSD. However, only in recent years positive changes following trauma and adversity have been studied systematically. These positive changes have been reported empirically following rape and sexual assault, military combat, natural disasters, plane crashes, shootings, bereavement, accidents, and injury. Furthermore, they have been reported after life events not typically associated with PTSD like chronic illness, heart attacks, breast cancer, bone marrow transplants, AIDS, recovery from substance addiction, and in the parents of children with disabilities (for reviews see Ai & Park, 2005; Helgeson, Reynolds, & Tomich, 2006; Linley & Joseph, 2004; Tedeschi & Calhoun, 2004; Zoellner & Maercker, 2006b). The definition of traumatic events in these studies is a bit broader and more inclusive than the more restrictive DSM-IV PTSD criteria. It is defined as circumstances that represent significant challenges to: (a) the individuals' ways of understanding the world and their place in it, (b) the adaptive resources of the individual (Janoff-Bulman, 1992; Maercker & Zoellner, 2004).

These positive changes have been labeled posttraumatic growth (PTG) even though different terms have been used to describe PTG (Tedeschi & Calhoun, 2004; Zoellner & Maercker, 2006b). Posttraumatic growth is defined as the subjective experience of positive psychological change reported by an individual as result of the struggle with trauma. As reviewed by Zoellner and Maercker (2006b), PTG has been conceptualized either as an outcome of coping with a traumatic event or a process. As *outcome* it is conceptualized as a multidimensional construct including changes in beliefs, goals, behaviors, and identity as well as the development of a life narrative and wisdom (Tedeschi & Calhoun, 2004). As a *process* it can be viewed as a meaning-making, interpretative coping process (Zoellner & Maercker, 2006b). Preliminary evidence suggests that at earlier stages of the trauma, PTG may reflect a coping process rather than an outcome that has emerged from the stressful event (Helgeson et al., 2006). Examples of positive psychological changes are: (1) an increased appreciation of life and setting of new life priorities, (2) a sense of increased personal strength, (3) identification of new possibilities, (4) more meaningful interpersonal relationships, or (5)

positive spiritual change (Tedeschi, Park, & Calhoun, 1998). These five domains of self-perceived growth can be measured using the Posttraumatic Growth Inventory (PTGI, Tedeschi & Calhoun, 1996), which represents a standardized and validated questionnaire. However, there are also other ways to assess growth and it is an ongoing debate, what may be the best way to assess it (for further information on PTG assessment see Cohen, Hetter, & Pane, 1998; Park & Lechner, 2006; Zoellner & Maercker, 2006b). A recent meta-analysis showed that the particular growth measure used, moderated the relation of growth to other outcomes (Helgeson et al., 2006).

2.8.2 Relation of posttraumatic growth to other variables

Empirical research has shown that PTG is associated with traits (e.g., positive affect, extraversion, openness to experience, optimism), coping styles (e.g., problem-focused coping, emotion-focused coping, acceptance coping, positive reinterpretation), and cognitive processing (e.g. rumination) (for reviews see Helgeson et al., 2006; Linley & Joseph, 2004; Maercker & Zoellner, 2004; Zoellner & Maercker, 2006b). However, there is no clear relationship between PTG and psychological distress (Helgeson et al., 2006; Zoellner & Maercker, 2006b). PTG has been found to be unrelated to PTSD (e.g. Zoellner, Rabe, Karl, & Maercker, 2008), or if related, then there was a positive relationship between the two (Helgeson et al., 2006; Tedeschi & Calhoun, 2004; Zoellner & Maercker, 2006b). In contrast, depressive symptoms were either unrelated or negatively related with PTG (Helgeson et al., 2006; Linley & Joseph, 2004; Zoellner & Maercker, 2006b). This is consistent with the view that PTG is not the same as an increase in general well-being or decrease in distress and growth and distress may be two independent dimensions of well-being (Joseph & Linley, 2005; Tedeschi & Calhoun, 2004). Thus, growth and emotional distress may well coexist for some people. Since there seems to be no direct link between growth and distress or health outcomes, several moderating variables have been suggested as: time since trauma, sex, and nature of stressor (Helgeson et al., 2006), dispositional optimism and religiosity (Milam, 2006), and trauma severity (Tomich & Helgeson, 2004). On the basis of these mixed results regarding the adaptive value of PTG and based on the available empirical evidence, Maercker and Zoellner (2004; 2006b) have suggested their “two-component-Janus-Face model” in which PTG is conceptualized as having two sides: (1) a functional, self-transcending or constructive side, and (2) an illusory, self-deceptive, or dysfunctional side. A recent empirical examination provided partial support for these assumptions (Zoellner et al., 2008).

2.8.3 Summary

In summary, the phenomenon of self-perceived PTG is still not well understood. There are different definitions (e.g. PTG as outcome or coping process) and no consistent criteria of these positive changes after trauma. Additionally, there is no clear relationship of PTG with adjustment variables. Thus, it is unclear what the construct PTG really measures. Although there is a great amount of research showing that self perceived posttraumatic growth exists in different trauma populations (Helgeson et al., 2006; Zoellner & Maercker, 2006b), there is an ongoing debate whether these reports of growth are valid, which means that they are linked to actual changes in a persons life (e.g. changes in behaviors, physical well-being) or whether reports of growth are illusionary (Park & Helgeson, 2006; Taylor, Kemeny, Reed, Bower, & Gruenewald, 2000; Zoellner & Maercker, 2006b). Recent empirical evidence have supported the latter assumption (Frazier et al., 2009; Frazier & Kaler, 2006; McFarland & Alvaro, 2000). However, time since the event seems to be an important moderator variable for the relation of PTG and adjustment (Helgeson et al., 2006). The broad definition of trauma in PTG research makes comparisons of findings even more difficult, since it is conceivable, that the perception of growth may differ for different kinds of traumata. Finally, there are almost no studies (see Epel, McEwen, & Ickovics, 1998, for exception) that relate measures of PTG to biological variables such as adaptive stress responses or underlying brain mechanisms. Clearly, there is need for research to examine growth from multiple perspectives (e.g. subjective, behavioral, biological, other objective changes) and from multiple points in time. Furthermore, the understanding of mechanisms (e.g. biological or psychological) through which positive changes occur remains elusive and needs further investigation. Here, research of hemispheric asymmetries and emotion (see next section) might be an interesting connection to PTG research. Because brain asymmetries have been associated with variables that have also been related to PTG, predictions about common mechanisms might be possible.

2.9 Hemispheric asymmetry and emotion

A substantial body of evidence suggests that the left and right cerebral hemispheres are differentially involved in emotion regulation and processing (for reviews see Debener, 2001; Demaree, Everhart, Youngstrom, & Harrison, 2005). First evidence for specialization of the two hemispheres of the brain for cognitive and emotional functions came from the study of patients with brain damage after stroke or brain surgery (Springer & Deutsch, 1998). For example early clinical observations had noticed that patients with right hemispheric lesions were often indifferent or emotionally flat (Babinski, 1914; Denny-Brown, Meyer, & Horenstein, 1952). These observations have later been supported by systematic study of hemispheric brain lesions (e.g. Gainotti, 1972). The following chapter provides a review of research and models on the hemispheric specialization of emotional processes, with emphasis on research of EEG asymmetries.

2.9.1 The right hemisphere model

The right-hemisphere hypothesis proposes that the right hemisphere is dominant for the experience and expression of emotions irrespective of valence (see reviews Gainotti, 1983; Heilman, Bowers, & Valenstein, 1985; Silberman & Weingartner, 1986). Evidence for this model comes mainly from studies of patients with brain damage in one hemisphere (see reviews Borod, 1992; Borod, Bloom, Brickman, Nakhutina, & Curko, 2002; Borod et al., 1996; Gainotti, Caltagirone, & Zoccolotti, 1993). The right-hemisphere hypothesis has been refined recently. In particular, it has been proposed that the right hemisphere might be dominant for the more “basic” levels of emotional arousal and automatic responses to emotional stimuli, whereas the left hemisphere might be specialized for functions of control and modulation of the spontaneous emotional response (Gainotti, 2000; Gainotti et al., 1993). These proposals are partly in line with hypotheses of contralateral inhibition in which one hemisphere regulates the activity of the other hemisphere and thus damage of one hemisphere disinhibits the other (e.g. Liotti & Tucker, 1995).

2.9.2 The valence model

The valence hypothesis states that the left hemisphere is specialized for experience and expression of positive emotions, whereas the right hemisphere is specialized for negative

emotions (e.g. Sackeim et al., 1982; Silberman & Weingartner, 1986). First evidence for these assumptions came from studies using the Wada test, the pharmacological deactivation of the left or right hemisphere. Deactivation to the left hemisphere usually produced a “depressive/catastrophic reaction” as described by (Goldstein, 1939) whereas deactivation to the right hemisphere produced euphoric behavior (for review see Silberman & Weingartner, 1986). Furthermore, lesion studies by Robinson and colleagues were of importance (Robinson & Downhill, 1995; Robinson, Kubos, Starr, Rao, & Price, 1984) showing that the severity of depression correlated significantly with proximity of the lesion to the frontal pole among patients with left anterior lesions. The valence model was partly integrated in other models which better explain inconsistencies in research e. g. on anger and psychopathology (see below).

2.9.3 The model of anterior asymmetry and emotion (AAE)

The valence hypothesis was largely subsumed by the approach-withdrawal model of emotion, which posits that each anterior hemisphere of the cortex is part of a specific affective/motivational brain system associated with the experience of emotion (Davidson, 1992, 1993, 1995, 1998a). However, Davidson acknowledged that the right posterior region might be specialized for emotion-perception irrespective of valence (Davidson, 1995). According to the AAE model, structures within the left prefrontal cortex are part of a circuit that processes emotions associated with approach behaviors and emotions. Conversely, the right anterior hemisphere is a major component within a brain circuit that is specialized for withdrawal behavior and activation of this system is associated with the experience of negative emotions (see Debener, 2001, for excellent review and empirical evidence) (see picture 1). The overlap between the valence and approach/withdrawal models is extensive, with most negative emotions (e.g., fear, disgust) eliciting withdrawal behavior and most positive emotions (e.g., happiness, amusement) are related to behavioral approach. However, e.g. anger - a negative emotion - has been also associated with approach behavior (see Harmon-Jones, 2004 for supporting evidence). In later developments of this model Davidson extended his formulations integrating subcortical components such as the amygdala, hippocampus, insula and anterior cingulate which clearly play a crucial role in specific functions of emotion and motivation (Davidson, 2003, 2004b; Davidson, Lewis et al., 2002; Davidson, Shackman, & Maxwell, 2004).

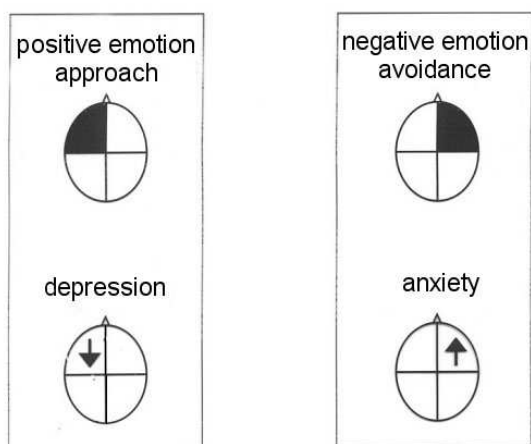


Figure 1. The model of anterior asymmetry and emotion by Davidson

Based on the AAE model there are several hypotheses that have been formulated. Individual differences in tonic frontal activation asymmetry are related to trait-like affective/motivational behaviors and dispositional affect. It has been proposed that anterior cortical baseline asymmetry represents a trait that functions as a diathesis. This diathesis predisposes an individual to respond with predominantly positive or negative affect given an appropriate emotion elicitor. This tendency of a person’s emotional reaction has been termed “affective style“. Thus, a person with tonic relative right-sided activation of the prefrontal cortex might show an increased vulnerability for the experience of negative emotions. In contrast, a person with relative left-anterior baseline activation might more easily experience positive emotions. According to the model, individuals with tonic relative left frontal hypoactivation should be more vulnerable for depression than those with the opposite asymmetry pattern (Davidson, 1995, 1998b). Regarding emotional states, the left anterior region should be more activated during experience of an approach related emotion and the right should be more activated during withdrawal-related emotion. The empirical examination of these hypotheses has most frequently used the EEG as a measure of brain activation, with activity in the alpha band (8–13 Hz). Alpha, however, is generally thought to be inversely related to brain activation (for methodological discussion please see Box 3).

Box 3. Methodological considerations in EEG alpha asymmetry research

There are a number of methodological issues that are crucial in EEG alpha asymmetry research. (for a detailed discussion see Allen, Coan, & Nazarian, 2004; Davidson, Jackson, & Larson, 2000; Debener, 2001; Hagemann, 2004; Hagemann, Naumann, & Thayer, 2001). The advantage of EEG measures is that it is a relatively inexpensive and completely non-invasive measure of brain activity and makes it ideally suited for the study of large samples on repeated occasions.

Reliability of EEG alpha asymmetry. Several studies suggested that baseline asymmetry measures of healthy subjects appear to be very reliable with estimated reliability coefficients in the .90s (internal consistencies), whereas retest correlations are somewhat lower (in the .50s or .60s for time intervals between 2 and 6 weeks) (Debener et al., 2000; Hagemann, Hewig, Naumann, Seifert, & Bartussek, 2005; Papousek & Schuller, 1998; Tomarken, Davidson, Wheeler, & Kinney, 1992; Towers & Allen, 2009).

Validity of EEG alpha asymmetry. The validity of EEG alpha activity as an indicator of cortical activation (EEG alpha activity is supposed to be inversely related to cortical activation) has been shown in studies using neuropsychological tasks of known hemispheric specialization (e.g. Davidson, Chapman, Chapman, & Henriques, 1990; Henriques & Davidson, 1997; Rabe, 2001 for review; Rabe, Debener, Brocke, & Beauducel, 2005). Furthermore, EEG alpha has been shown to be inversely related to brain activation using PET (e.g. Cook, O'Hara, Uijtdehaage, Mandelkern, & Leuchter, 1998). However, EEG alpha activity measures reflect measures of activity of rather broad cortical regions of the brain (Davidson, Jackson et al., 2000).

The choice of the EEG reference. One major problem in EEG asymmetry research is the choice of the reference, since the EEG is a difference measure between the active site and the reference site. The linked-earlobes/mastoids reference has been recommended because it is currently the most often used method and its convergent validity with other reference schemes has been demonstrated: e.g. nose reference (Debener, 2001) or current source density (Debener, 2001; Hagemann et al., 2005). Furthermore it has been suggested to use multiple reference schemes (Davidson, Jackson et al., 2000; Hagemann et al., 2001).

Within both approach/withdrawal model and valence model, frontal EEG asymmetry has been associated with both trait-like and state-dependent processes (for extensive reviews see Coan & Allen, 2003b; Coan & Allen, 2004; Debener, 2001). The vast majority of work in this area focuses on frontal activation asymmetry as a trait measure (baseline EEG), which has been associated with: (1) other psychological traits, (2) psychopathology, and (3) affective responding. Furthermore, frontal EEG asymmetries have been measured during affective states.

Trait frontal EEG asymmetry and other trait-like measures

Frontal EEG asymmetry is thought to be associated with personality traits related to the approach/withdrawal concept. Several researchers have identified a relationship between

frontal baseline EEG asymmetry and motivational traits such as behavioral inhibition and activation (BIS and BAS, respectively) (Coan & Allen, 2003a; Harmon-Jones & Allen, 1997; Sutton & Davidson, 1997), with greater support for the association with the BAS (Coan & Allen, 2003a; Harmon-Jones & Allen, 1997). Furthermore, left frontal activation was associated with trait anger, a negatively-valenced but approach-related emotion (Harmon-Jones & Allen, 1998). Together, these findings give support for the relative independence of the approach/withdrawal and valence continuums (for discussion see Harmon-Jones, 2004). Additionally, frontal EEG asymmetry has been related with other self-report measures, like general positive and negative affect (PA and NA, respectively), social behavior tendencies like shyness and sociability (Schmidt, 1999), sensation seeking (Santesso et al., 2008), repressive coping style (Kline, Allen, & Schwartz, 1998; Tomarken & Davidson, 1994), and psychological well being (Urry et al., 2004). However, there are also contradictory results (Hagemann et al., 1999).

In addition, interesting studies in monkeys and humans have shown that frontal brain asymmetry is related to other physiological traits and reactions involved in stress responses like cerebrospinal fluid concentrations of corticotrophin-releasing hormone (CRH, Kalin, Shelton, & Davidson, 2000), cortisol levels and reactions (Buss et al., 2003; Hewig et al., 2008; Kalin, Larson, Shelton, & Davidson, 1998), and certain immune responses (Davidson, Coe, Dolski, & Donzella, 1999; Kang et al., 1991; Master et al., 2009).

Trait frontal EEG asymmetry and psychopathology

A core hypothesis within the AAE is that tonic frontal activation asymmetry represents a diathesis towards depression, in particular, individuals with relative left frontal hypoactivation should be more vulnerable for mood disorders than those with the opposite asymmetry pattern (Davidson, 1998b). Supporting evidence comes from a number of studies with clinically depressed subjects (e.g. Allen, Iacono, Depue, & Arbisi, 1993; Debener et al., 2000; Deslandes et al., 2008; Gotlib, Ranganath, & Rosenfeld, 1998; Henriques & Davidson, 1991), previously depressed (Gotlib et al., 1998; Henriques & Davidson, 1990), and subclinical depression samples (Accortt & Allen, 2006; Debener, 2001). Furthermore, there is evidence of stability in EEG asymmetry in depression regardless of clinical state (Allen et al., 1993; Allen, Urry, Hitt, & Coan, 2004) as well as first evidence for the diathesis formulation in a longitudinal study (Blackhart, Minnix, & Kline, 2006). However, there have been results inconsistent with Davidson's model (Bruder, 2003 for review ; Bruder et al., 1997; Kentgen et

al., 2000; Miller et al., 2002; Reid, Duke, & Allen, 1998). Studies of resting EEG asymmetries in anxiety disorders have produced rather mixed results. There have been no differences, as compared to a control group, in frontal baseline brain asymmetry for PTSD patients (McCaffrey, Lorig, Pendrey, McCutcheon, & Garrett, 1993; Metzger et al., 2004; Shankman et al., 2008) and social phobia (Davidson, Marshall, Tomarken, & Henriques, 2000), but panic patients (Wiedemann et al., 1999). For a recent critical meta-analytic review of frontal EEG asymmetry research in depression and anxiety please see Thibodeau, Jorgensen, and Kim (2006).

Trait frontal asymmetry as predictor of affective style

According to the AAE model tonic anterior asymmetry is hypothesized to predict affective responses to emotional stimuli. Support for this assumption comes from studies showing that EEG alpha asymmetry predicts affective responses to emotional film clips (Tomarken, Davidson, & Henriques, 1990; Wheeler, Davidson, & Tomarken, 1993), affective responses to sport (Petruzzello, Hall, & Ekkekakis, 2001; Petruzzello & Landers, 1994; Petruzzello & Tate, 1997), emotional associations (Sutton & Davidson, 2000), and adaptive emotion regulation (Jackson et al., 2003). However, there are failures in replication of these findings (Davidson, 1998b for discussion; Gotlib et al., 1998; Hagemann, Hewig, Naumann, Seifert, & Bartussek, 2005; Hagemann, Naumann, Becker, Maier, & Bartussek, 1998).

Frontal EEG activation asymmetry as a state measure of emotion

A direct approach to investigate lateralized brain activation is to measure EEG asymmetry during emotion-eliciting conditions. According to the AAE model, stimuli that encourage approach responses should result in relatively greater left frontal activation. In contrast, environmental stimuli that promote withdrawal responses should result in relatively greater right frontal activation. Changes in EEG alpha asymmetry have been observed in healthy subjects during a variety of emotional stimuli such as depressive or euphoric mood induction (Tucker, Stenslie, Roth, & Shearer, 1981), emotional film clips (Davidson, Ekman, Saron, Senulis, & Friesen, 1990), anger induction (Harmon-Jones & Sigelman, 2001; Harmon-Jones, Vaughn-Scott, Mohr, Sigelman, & Harmon-Jones, 2004), voluntary facial expressions (Coan, Allen, & Harmon-Jones, 2001), pleasant and unpleasant odors (Kline, Blackhart, Woodward, Williams, & Schwartz, 2000), cigarette deprivation (Zinser, Fiore, Davidson, & Baker, 1999), happiness/anger (Waldstein et al., 2000), reward/punishment (Sobotka, Davidson, & Senulis,

1992), exam stress (Lewis, Weekes, & Wang, 2007), and motivational manipulations (Miller & Tomarken, 2001).

With regard to clinical samples, Wiedemann et al. (1999) found relative right frontal activation during rest and confrontation with anxiety-related pictures in panic patients. Comparable findings of relative right-sided activation in anterior-temporal, lateral-frontal, and parietal regions were reported by Davidson, Marshall, Tomarken, and Henriques (2000) in a sample of social phobics during the anticipation of a public speech. However, there have also been findings inconsistent with the AAE model (Heller, Nitschke, Etienne, & Miller, 1997).

Summary

In summary, there is a large body of evidence for the AAE model which has inspired extensive research on EEG asymmetries (Allen & Kline, 2004). There is also supporting evidence for lateralized brain function and emotion in studies using functional neuroimaging techniques (Murphy, Nimmo-Smith, & Lawrence, 2003; Pizzagalli, Shackman, & Davidson, 2003; Wager, Phan, Liberzon, & Taylor, 2003). However, only a few neuroimaging studies have directly tested assumptions of models of hemispheric asymmetry (e.g. Canli, Desmond, Zhao, Glover, & Gabrieli, 1998; Herrington et al., 2005; Nitschke, Sarinopoulos, Mackiewicz, Schaefer, & Davidson, 2006; Pagani et al., 2005). A major problem in interpreting hemispheric findings in functional neuroimaging studies is that neuroimaging studies examining hemispheric brain asymmetries often display methodological inadequacies (Davidson & Irwin, 1999; Pizzagalli et al., 2003). Davidson and Irwin (1999) argued that in most neuroimaging studies interpretations about asymmetric activation were made on the basis of voxels in one hemisphere that exceeded statistical threshold while homologous voxels in the opposite hemisphere did not. However, such an analytic strategy tests only for the main effects of the condition. Accordingly, hemispheric differences in activation should be examined with appropriate statistical tests involving interactions with the factor “Hemisphere”.

2.9.4 The integrative Model

A model that might explain some inconsistencies in the study of brain asymmetries in relation to emotion and psychopathology has been suggested by Heller and colleagues (Heller, 1990, 1993; Heller & Nitschke, 1997), and subsequently refined (Heller et al., 2003; Heller & Nitschke, 1998; Heller et al., 1997; Heller, Schmidtke, Nitschke, Koven, & Miller, 2002;

Nitschke, Heller, & Miller, 2000; Nitschke, Heller, Palmieri, & Miller, 1999). This neuropsychological model of emotion integrates in part the competing right hemisphere hypothesis (Gainotti et al., 1993) and the valence hypothesis (Davidson, 1992). Based on behavioral, neuropsychological, and psychophysiological data the model incorporates psychological theories of emotion decomposing emotional states into two components, valence and arousal. The model proposes that the valence dimension (pleasant, unpleasant) is dependent on functions of anterior regions of the cortex. When the left frontal region is active relative to the right, affective valence is pleasant, whereas relative right-frontal activity is associated with negative affect. Furthermore, the model posits that the arousal dimension depends on right posterior regions of the brain. Nitschke et al. (2000) proposed that the right posterior anxious arousal system promotes sympathetic nervous system activity, spatial attention, visual scanning of the environment, and sensitivity to meaningful nonverbal cues. According to the model, anxiety and depression are associated with different patterns of brain activity in right posterior regions, with anxiety to be associated with increased and depression with decreased activity (see figure 2).

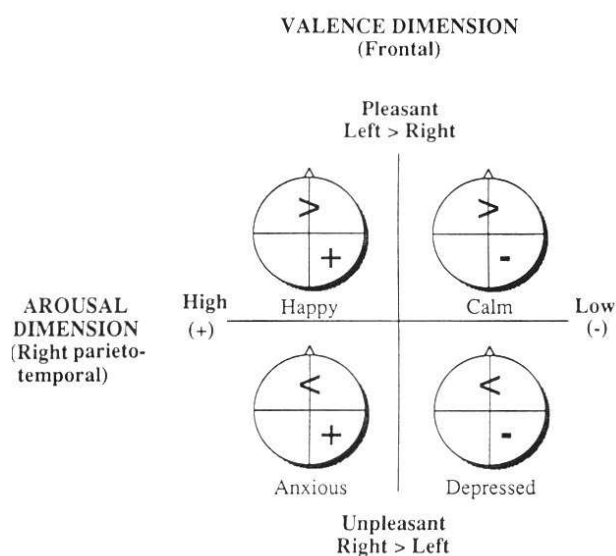


Figure 2. The neuropsychological model of emotion by Heller and colleagues

This model explained some inconsistencies of prior EEG asymmetry research in depression and anxiety (Bruder et al., 1997; Kentgen et al., 2000; Metzger et al., 2004). Empirical evidence for the model comes from two studies investigating depressed patients (Keller et al., 2000) and students with high and low levels of depression (Heller, Etienne and Miller, 1995; Keller et al., 2000) using a neuropsychological task measuring a hemispheric

bias for face processing. Consistent with their predictions they found greater left hemisphere activation specific to depression whereas anxiety was associated with larger right hemisphere activation. Two EEG studies gave further support for the hypothesis of right posterior hypoactivation in depression using neuropsychological verbal and spatial tasks during EEG measurement (Henriques & Davidson, 1997; Rabe, Debener, Brocke, & Beauducel, 2005). However, in an EEG study of brain activity in anxiety and depression findings inconsistent with the assumptions have been observed (Heller et al., 1997).

In a refinement of their theory Heller, Nitschke, Etienne, and Miller (1997) proposed a distinction between subtypes of anxiety related to different patterns of brain activation. Anxious arousal (e.g. panic, state anxiety, and sympathetic nervous system hyperreactivity) should be associated with greater right parieto-temporal activation, while anxious apprehension (e.g. worry, rumination, anticipation of future threat) should be associated with greater left anterior activity since it involves linguistic processing (for review, see Heller et al., 2003; Heller et al., 2002; Nitschke et al., 2000). Partial support for their assumptions comes from studies examining regional EEG asymmetry in self-reported anxious arousal (Nitschke et al., 1999) and during experimentally manipulated anxious-arousal (Heller et al., 1997).

The assumptions of Heller and colleagues have their strengths in explaining some inconsistencies observed in findings with depression and anxiety. However, there is only limited research directly testing their assumptions. Furthermore, the model does not define: (1) a clear distinction between state and trait of emotion (valence or arousal). Additionally, it does not readily explain the incompatible relation between anxious apprehension and negative valence (for critical review see Debener et al., 2000).

2.9.5 Summary

In summary, the different models of brain asymmetry and emotion each are strong in explaining different components of emotion (e.g. perception, experience, expression, and arousal). The right-hemisphere model emphasizes emotional perception and expression. The valence model, which is mainly focusing on experience of emotion, was subsumed by the AAE model of emotion which has probably the most empirical support. The AAE model is probably the most elaborated allowing clear predictions (e.g. about trait asymmetry as diathesis variable) and thus enables good empirical evaluation. The integrative model of Heller and colleagues confines the valence hypothesis to anterior brain regions and in part the

right-hemisphere hypothesis to posterior regions. Its strength is the integration of seemingly discrepant findings regarding different types of anxiety and comorbidity of anxiety and depression. As reviewed above and in chapter 2.6.1, there is only little research directly investigating brain asymmetries in PTSD. However, theories of brain asymmetry and emotion make clear predictions about emotional processes as avoidance, arousal and negative valenced emotions which are key features of PTSD. Furthermore, the link of asymmetry research could help answering some important questions regarding the specificity of PTSD among anxiety disorders and comorbidity with depression. Furthermore, as reviewed above, especially trait frontal asymmetry has been associated with positive emotion and psychological well-being, constructs which are also related to PTG. Thus, research is warranted investigating the possible link between PTG and frontal brain asymmetry, which might be useful for increasing construct validity of PTG and the understanding of mechanisms associated with the development of PTG.

2.10 Research questions

PTSD is a highly distressing condition emerging in the aftermath of traumatic events such as MVAs. As reviewed, theories of brain asymmetry and emotion have proposed that asymmetries of brain activation are related to certain features of human emotion (e.g. valence, motivational tendencies, and arousal). Based on these models one might predict that certain features of PTSD (e.g. negative affective responses, avoidance tendencies, and hyperarousal) are associated with asymmetrical brain activation/activity. However, there are only few studies that directly investigated EEG asymmetries in PTSD during rest (Metzger et al., 2004; Shankman et al., 2008) or emotion-eliciting conditions (McCaffrey et al., 1993) with mixed results. Thus, the first goal (study I) of the present thesis was to systematically investigate EEG alpha asymmetry during rest and during the presentation of emotional (neutral, positive, negative, and trauma-related) pictures in survivors of MVAs with PTSD and with subsyndromal PTSD. The results of patients were compared to two control groups: MVA survivors without PTSD as well as healthy controls without severe accidents. We were interested in the question whether patients with PTSD or subsyndromal PTSD after severe MVAs show an abnormal pattern of EEG alpha asymmetry which might explain certain features of PTSD such as avoidance tendencies or hyperarousal.

As reviewed above, there is only little knowledge about brain mechanisms that may underlie reductions in PTSD symptoms due to psychological therapy, especially CBT. Thus, goal of study II was to evaluate whether a reduction of PTSD severity due to successful cognitive behavioral therapy for MVA-related PTSD is associated with change in EEG alpha asymmetry during trauma-related stimulation. Therefore, we measured EEG activity before and after CBT (in comparison to an assessment-only Wait-list condition) as part of a previously completed controlled, randomized treatment trial for MVA-related PTSD (Maercker et al., 2006).

As described, the systematic study of positive changes of trauma as PTG has emerged in recent years. This research has led to identification of psychological factors that may promote PTG. However, neurobiological correlates of PTG are almost unknown. Based on models of brain asymmetry and emotion and previous findings showing a relation with relative left cortical anterior activity with constructs that may be related to PTG (e.g. positive affect and well-being) a relation of brain asymmetry and PTG is conceivable. Thus, aim of study III was to examine the relationship between anterior EEG alpha asymmetry and subjective perception of posttraumatic growth in MVA survivors.

3 The empirical studies

3.1 Study I: Regional brain electrical activity in posttraumatic stress disorder after motor vehicle accidents*

3.1.1 Introduction

EEG asymmetries have been associated with motivational and affective traits and states (Coan & Allen, 2003b). Davidson (1995) assumes in his model of anterior asymmetry and emotion that certain regions within the left hemisphere are involved in approach-related behavior and emotion, whereas right prefrontal and anterior temporal regions have been proposed to be related to withdrawal-related behavior and emotion. Evidence for the model comes from research investigating frontal EEG asymmetry in relation to emotional/motivational traits (Tomarken, Davidson, Wheeler, & Doss, 1992) and emotional responding (Wheeler et al., 1993), although Hagemann, Naumann, Becker, Maier, and Bartussek (1998) failed to replicate these relationships. Frontal baseline EEG asymmetry has also been associated to psychopathology such as depression (Gotlib et al., 1998; Henriques & Davidson, 1991). For pathologic anxiety, Wiedemann et al. (1999) found relative right frontal activation during rest and confrontation with anxiety-related pictures in panic patients. Comparable findings of relative right-sided activation in anterior-temporal, lateral-frontal, and parietal regions were reported by Davidson, Marshall, Tomarken, and Henriques (2000) in a sample of social phobics during the anticipation of a public speech.

However, a number of studies investigating brain asymmetries in relation to psychopathology showed results inconsistent with Davidson's model (Bruder et al., 1997; Reid et al., 1998). Heller and colleagues (e.g. Heller & Nitschke, 1998) proposed an alternative model in which anterior cortical regions are involved in the modulation of valence whereas the right parieto-temporal region is involved in the modulation of emotional arousal. It is suggested that depression is associated with right parieto-temporal hypoactivation, whereas emotional arousal is related to hyperactivation of the same region. Evidence for the model comes from studies investigating depressed patients (Keller et al., 2000) and students

* This study is already published (Rabe, Beauducel, Zöllner, Maercker, & Karl, 2006). Reprint of content with permission of the American Psychological Association.

with high and low levels of depression and anxiety (Heller, Etienne, & Miller, 1995; Keller et al., 2000).

In a refinement of their theory Heller, Nitschke, Etienne, and Miller (1997) proposed a distinction between subtypes of anxiety related to different patterns of brain activation. Anxious arousal should be associated with greater right parieto-temporal activation, while anxious apprehension (e.g. worry and rumination) should be associated with greater left anterior activity. Support for their assumptions comes from studies examining regional EEG asymmetry in self-reported anxious arousal (Nitschke et al., 1999) and during experimentally manipulated anxious-arousal (Heller et al., 1997).

To our knowledge there are only two studies directly investigating EEG asymmetries in PTSD. One study reported right-sided activation in response to trauma-related olfactory stimuli in a small sample ($n = 5$) of Vietnam veterans with PTSD (McCaffrey et al., 1993). Recently, Metzger et al. (2004) reported that PTSD arousal symptoms were associated with increased relative right parietal baseline activity in a sample of female Vietnam War nurse veterans. However, it remained unclear if the observed relations could be explained by differences in the emotional state during baseline, since it was not assessed in this study. Interestingly, the amount of depression symptoms did not attenuate posterior asymmetry but rather was associated with increased relative right parietal activity.

In the current study, we examined brain electrical activity during rest and during the presentation of emotional pictures (neutral, positive, negative, trauma-related) in MVA survivors with PTSD, subsyndromal PTSD, and without PTSD as well as healthy controls without severe accident. Patients with PTSD and subsyndromal PTSD are characterized by symptoms of anxiety, avoidance, hyperarousal, and display psychological distress to trauma-related cues. Based on research highlighting the role of right anterior regions in withdrawal related emotions and right posterior regions in anxious arousal we expected that persons with PTSD and subsyndromal PTSD would exhibit increased activation (EEG alpha reduction) of right hemisphere anterior and posterior regions during exposure to a trauma-related picture. We did not have specific hypotheses about other emotion conditions. Based on research highlighting the role of resting brain activity as a trait-marker for psychopathology, we assumed that PTSD and subsyndromal PTSD patients would show increased relative right anterior and posterior baseline activity. It has been proposed that depression and anxious arousal might produce opposing effects on posterior asymmetry. Since there is a large number

of PTSD patients with comorbid depression (Kessler et al., 1995) it was important to rule out whether comorbid depressive symptoms might attenuate right posterior activation.

3.1.2 Methods

Participants and assessments

Survivors of MVAs and controls without MVAs were recruited for a treatment study through self-referral local media coverage and advertising. Subjects were included when the accident dated at least 6 months. Exclusion criteria were a history of neurological problems such as epilepsy, brain surgery, brain damage or severe head injury during the accident. Furthermore, we excluded subjects with current alcohol and/or substance abuse or dependence, current or past schizophrenic, bipolar, or psychotic disorder. All participants were required to be off all psychotropic medication for at least 1 month before testing. All participants were right-handed as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971).

Diagnostic procedure. All participants received a comprehensive description of the study and provided written informed consent at the initial diagnostic assessment. Participants were assessed by advanced doctoral and diploma students in clinical psychology who had received extensive training in the assessment procedures. The diagnostic session was tape-recorded and lasted 2-3 hours including an accident interview and clinical interviews.

Injury severity. Injury severity was assessed by the Injury Severity Score (ISS) that was abstracted from medical records using the Abbreviated Injury Scale (AIS90, AAAM, 1990). The ISS is defined as the sum of the squares of the highest scores on the AIS 90 for each of the three most severely injured body regions.

Clinician Administered PTSD Scale (CAPS, Blake et al., 1995). This scale represents a standardized method that allows generating categorical diagnosis of current and lifetime PTSD as well as a total score obtained by summing the ratings of frequency and severity of each of the 17 PTSD symptoms as defined in the Diagnostic and Statistical Manual of Mental Disorders (4th ed.; DSM-IV; American Psychiatric Association, 1994). For analytic purposes, we averaged the scale items corresponding to 4 PTSD dimensions: Reexperiencing (5 items), Avoidance (2 items), Numbing (5 items), and Hyperarousal (5 items). Splitting the Avoidance/Numbing cluster has been performed based on theoretical considerations regarding our hypotheses and empirical work showing that these two dimensions diverge as differentiable dimensions (Asmundson et al., 2000). In this study we used a German version of the CAPS (Schnyder & Moergeli, 2002) with comparable reliability and validity as the

English version. In this sample Cronbach's coefficient alpha was .89, .74, .61, .77, and .74 for the CAPS Total Score and the dimensions Reexperiencing, Avoidance Numbing, and Hyperarousal, respectively. A good diagnostic agreement (kappa of .82, $p < .001$) was established by rescoring (conducted by psychologists blinded to the diagnosis) the CAPS proportion of a randomly selected subsample ($n = 18$) of interviews.

Structured Clinical Interview for the DSM-IV (SCID) (First, Spitzer, Gibbon, & Williams, 1996; German version by Wittchen, Wunderlich, Gruschwitz, & Zaudig, 1997). The SCID evaluated the presence of concurrent and lifetime DSM-IV Axis I disorders. We administered all Axis I modules of the standard SCID with exception of the PTSD module.

Self report measures. We used a German version (Hautzinger, Bailer, Worall, & Keller, 1994) of the Beck Depression Inventory (BDI) (Beck & Steer, 1987). The BDI is a 21 item self rating scale which was designed to measure the presence and severity depressive symptoms with good reliability (Cronbach's $\alpha = .90$) in this sample. The German version (Laux, Glanzmann, Schaffner, & Spielberger, 1981) of the State-Trait Anxiety Inventory (STAI) (Spielberger, Gorsuch, & Lushene, 1970) is a 20-item self report measure scoring for cognitive and affective components of both state anxiety and trait anxiety (STAI-T, $\alpha = .94$ in this sample). Self reported state and trait positive affect (PA) and negative affect (NA) were assessed by an extended (24-items) German version (Krohne, Egloff, Kohlmann, & Tausch, 1996) of the Positive and Negative Affect Schedule (PANAS) (Watson, Clark, & Tellegen, 1988). Cronbach's alpha values for PANAS state ranged from .84 to .92 for PA and from .80 to .92 for NA.

Subject characteristics. Based on the CAPS the MVA victims were classified into three groups: full PTSD, subsyndromal PTSD, and non-PTSD. Patients with full PTSD were required to meet all three symptom clusters (B through D) for PTSD according to DSM-IV criteria. We also diagnosed individuals as subsyndromal PTSD if they met the DSM-IV cluster B (Reexperiencing) and either cluster C (Avoidance/Numbing) or cluster D (Hyperarousal) following the most prominent definition of subsyndromal PTSD proposed by Blanchard and colleagues (e.g. Blanchard, Hickling, Taylor et al., 1996). Similarly to PTSD patients, persons with subsyndromal PTSD were also required to meet the criterion F (experience distress because of their PTSD symptoms). All of the 21 subsyndromal PTSD patients met the cluster B (Reexperiencing). Twenty patients met additionally the cluster D (Hyperarousal) and only one the cluster C (Avoidance/Numbing). Subsyndromal or partial PTSD has been shown to constitute a significant proportion of MVA victims that is clinical

meaningful and associated with significant distress (Marshall et al., 2001; Schuetzwohl & Maercker, 1999). The non-PTSD group was required to meet either no cluster or one but not criterion F.

Seventy MVA survivors were included in the current study. Twenty four met the DSM-IV criteria for full PTSD, subsyndromal PTSD (n = 23), and non-PTSD (n = 23). Additionally, 28 non-traumatized healthy controls (HC) without a history of any severe accident or other trauma participated. HC's were required to have an absence of current or past DSM-IV axis I psychopathology according to the SCID. The data sets of 2 patients with full PTSD, 2 with subsyndromal PTSD, 2 non-PTSD, and 5 healthy controls were excluded because of an insufficient amount of artifact free EEG data in one of the recording conditions. The resulting final sample comprised patients with full PTSD (n = 22), subsyndromal PTSD (n = 21), non-PTSD (n = 21), and HC (n = 23).

Based on the SCID interview, 9 PTSD patients fulfilled criteria for current major depression (MDD) and 4 PTSD patients fulfilled criteria for lifetime but not current MDD. Additional diagnoses in the PTSD group were current dysthymia (n = 2), panic disorder without agoraphobia (n = 2); panic disorder with agoraphobia (n = 1), agoraphobia without panic disorder (n = 2), social phobia (n = 2), specific phobia (n = 5), lifetime generalized anxiety disorder (n = 1), and obsessive compulsive disorder (n = 1). Additional diagnoses in the subsyndromal PTSD group were MDD (n = 4), agoraphobia without panic disorder (n = 1), social phobia (n = 2), and specific phobia (n = 1). Lifetime but not current diagnoses in the non-PTSD group were MDD (n = 6), panic disorder without agoraphobia (n = 1), social phobia (n = 1). Two of the non-PTSD participants met the criteria for mild current specific phobia.

As can be seen in Table 1 there were no significant differences between the diagnostic groups in age, degree of right handedness, time since the accident, concussion, loss of consciousness, injury severity, and gender although on a descriptive level non-PTSD controls had a larger percentage of males. Based on the CAPS values one would characterize the subsyndromal PTSD group as one with a high level of Reexperiencing and Avoidance symptoms, usually Hyperarousal symptoms but essentially no Numbing symptoms.

Table 1: Means, Standard Deviations, and Significance Tests for Diagnostic and Demographic Characteristics of the Diagnostic Groups

Characteristics	Healthy Controls	Non-PTSD with MVA	Subsyndromal PTSD	PTSD	Test	p
N	23	21	21	22		
Gender (N)						
Male/Female	7/16	10/11	7/14	3/19	$\chi^2(3) = 5.89$.12
% female	70	52	67	86		
Age (years) (M, SD)	37.65 ^x (10.72)	43.05 ^x (16.63)	35.76 ^x (9.82)	42.50 ^x (11.64)	F(3,83) = 1.79	.16
Handedness (M, SD)	74.92 ^x (29.39)	70.66 ^x (31.82)	83.22 ^x (23.69)	77.93 ^x (31.33)	F(3,83) = 0.90	.41
Months since MVA (M, SD) -		66.86 ^x (92.05)	39.76 ^x (36.81)	77.95 ^x (104.51)	F(2,61) = 1.18	.31
Injury Severity Score (M,- SD)		13.33 ^x (12.67)	6.62 ^x (5.99)	13.18 ^x (11.17)	F(2,61) = 2.90	.06
Concussion (N)						
(without/with)	-	18/3	17/4	14/8	$\chi^2(2) = 3.25$.20
Loss of consciousness (N)						
Without/With	-	11/10	13/8	12/10	$\chi^2(2) = .43$.81
PTSD Symptoms (CAPS)						
CAPS Total Score (M, SD) -		6.10 ^x (4.53)	33.05 ^y (10.92)	56.45 ^z (11.26)	F(2,61) = 152.37	<.001
Reexperiencing (M, SD) -		1.81 ^x (2.36)	12.62 ^y (6.00)	14.86 ^y (5.48)	F(2,61) = 43.20	<.001
Avoidance (M, SD) -		0.57 ^x (1.33)	5.81 ^y (3.40)	6.55 ^y (3.80)	F(2,61) = 24.12	<.001
Numbing (M, SD) -		1.57 ^x (2.94)	2.57 ^x (3.60)	15.86 ^y (5.97)	F(2,61) = 71.21	<.001
Hyperarousal (M, SD) -		2.14 ^x (2.26)	12.05 ^y (6.59)	19.18 ^z (4.00)	F(2,61) = 71.21	<.001
BDI (M, SD)	3.61 ^x (4.64)	5.50 ^x (5.42) ^a	11.45 ^y (7.76) ^a	22.82 ^z (9.69)	F(2,61) = 73.27	<.001
STAI-T (M, SD)	35.26 ^x (7.42)	34.85 ^x (9.30) ^a	44.45 ^y (7.82) ^a	54.27 ^z (10.77)	F(2,61) = 23.00	<.001

BDI = Beck Depression Inventory Depression, STAI-Trait = State-Trait Anxiety Inventory - Trait Scale, CAPS = Clinician-Administered PTSD Scale, Handedness was measured by the Edinburgh Handedness Inventory (Oldfield, 1971), with scores ranging from -100 (strong left hand preference) to 100 (strong right hand preference). ^a N = 20, ^{x, y, z} Means within a column which share a superscript do not differ at p = 0.05 (Tukey Test)

Procedure

EEG was recorded in an electrically shielded room with dim light while participants were resting in a comfortable arm chair. First, EEG baseline data were recorded. The recording procedure was kept similar to Tomarken, Davidson, Wheeler, and Kinney (1992). Participants were informed that there would be eight 1 min resting baselines, four with eyes open four with eyes closed and that they should try to minimize eye blinks and movements. Two randomly assigned, counterbalanced orders were used for eyes open (O) and eyes closed (C) trials of the resting baselines (C-O-O-C-O-C-C-O, O-C-C-O-C-O-O-C). Participants heard a tone indicating the beginning and a double tone indicating the end of each 1-min recording.

During the 20 s lasting breaks between the baselines, participants were informed via PC monitor whether the following period was eyes open or eyes closed. Immediately after the final resting period, baseline mood was assessed with the PANAS-state questionnaire. After the resting baselines, 4 phases of mood induction via picture presentation were conducted. The positive (two bunnies), negative (a barking dog), and neutral (spoon) pictures were taken from the International Affective Picture System (IAPS) (Lang, Öhmann, & Vaitl, 1988). The MVA-picture was an actual photograph from a crashed car lying on the roof. The sequence of the picture presentation phases was counterbalanced between participants. The picture presentation phases lasted 1 minute and were separated by intervals of 2 minutes. At the end of these conditions, participants rated their actual mood using the PANAS-state questionnaire. Following this procedure, an event-related-potential experiment (not reported here) was administered.

Electrophysiological recording and analysis

Electroencephalograms were recorded from 28 scalp placements (Fp1, Fp2, F7, F3, Fz, F4, F8, Fc5, Fc1, Fc2, Fc6, T7, C3, Cz, C4, T8, Cp5, Cp1, Cp2, Cp6, P7, P3, Pz, P4, P8, POz, O1, O2) according to the extended 10-20 system (Pivik et al., 1993) using a stretchable electro cap (FMS, Falk Minow Services, Munich, Germany). Moreover, we recorded EEG activity at linked mastoid positions (A1, A2). All sites were referenced to a computer averaged F3/F4 reference and grounded at AFz. Impedances were maintained below 5 k Ω and within 500 Ω at homologous sites. The EEG signal was recorded by a Nihon Kohden amplifier (NeuroFileII system), filtered with a time constant: 10 s and a high frequency cut-off (300 Hz) and digitized online at 1024 Hz and stored at 256 Hz. Additionally, we recorded electromyographic activity (EMG), electrodermal activity (EDA), and the electrocardiogram (ECG). The data of these measures are not presented here.

A linked-mastoids reference was rederived offline. Physically linking the mastoids has been theoretically criticized of producing a low resistive shunt between the two sides of the head (for discussion see Hagemann, 2004). However, empirical evidence suggests that there is no difference between physically and computer-averaged ears (Senulis & Davidson, 1989). EEG artifacts (eye blinks and muscle artifacts) were removed by applying the independent component analysis (ICA) (Jung et al., 2000) to the EEG segments of interest. Prior to artifact screening, an offline bandpass filter (1 to 30 Hz) was applied. Continuous EEG data were divided offline in 4 s epochs (50 % overlap) and again visually inspected for artifacts. The

percentage of accepted epochs in this study was $M = 93.06$ ($SD = 10.01$) for the baseline eyes closed condition, $M = 81.01$ ($SD = 21.20$) for the baseline eyes open condition, $M = 70.21$ ($SD = 26.53$) for the neutral picture, $M = 75.54$ ($SD = 23.81$) for the positive picture, $M = 73.44$ ($SD = 25.22$) for the trauma-related picture, and $M = 76.36$ ($SD = 25.12$) for the negative picture. The percentage of accepted epochs did not differ between diagnostic groups ($p > .11$). All epochs free of artifacts were subjected to a fast Fourier transformation (FFT) using a Hamming window over the distal 50% of each epoch. By averaging segments, estimates of spectral power (μV^2) were derived for 0.25 Hz bins, averaged between 8-13 Hz, and normalized (natural log) to obtain \ln power density ($\ln \mu V^2/Hz$) in the alpha band (Gasser, Bächer, & Möcks, 1982).

Statistical analysis

The analytic strategy to assess alpha asymmetry was to quantify activity recorded over four brain regions: left anterior, right anterior, left posterior, right posterior. We therefore averaged electrode sites within anterior (left: F3, F7, T7; right: F4, F8, T8) and posterior (left: Cp5, P3, P7; right: Cp6, P4, P8) regions. This has the advantage of reducing the amount of data and according to the Spearman-Brown prophecy formula increases reliability of anterior and posterior brain asymmetry measures. The four quadrants of the scalp were included into statistical analyses. To examine the hypothesized asymmetries we computed repeated-measures multivariate analysis of variance (MANOVA) using Pillai's correction with the within-subject factors Hemisphere (left, right), Region (anterior, posterior) and the between-subject-factors Group (HC, non-PTSD, subsyndromal PTSD, PTSD) and Gender (Female, Male). For the baseline an additional within-subject factor Baseline-Condition (eyes open, eyes closed) was used.

To assess brain asymmetry during the emotion conditions we adopted an approach similar to that of Davidson, Marshall et al. (2000). In order to examine the emotion-induced activation relative to the neutral condition we computed neutral-minus-emotion-condition change scores by subtracting alpha activity during the three emotional conditions (positive, negative, trauma-related) from that of the neutral condition. A decrease in alpha power is assumed to reflect increased activity. Thus, positive change scores indicate greater activation during emotion condition compared to neutral condition. All reported effects are based upon these change scores. This approach has the advantage of controlling individual differences in the total amount of recorded alpha power e.g. produced by individual differences in skull

thickness. Differences in alpha power change scores were investigated using MANOVAs including Emotion-Condition (positive, negative, trauma-related) as additional within-subject factor. Based on our prediction that groups differ in regional alpha asymmetry during certain conditions significant interactions involving Group, Hemisphere, and Condition were followed by separate MANOVAs. Furthermore, simple-effect MANOVAs were conducted for each group separately to test our specific predictions of hemispheric (left vs. right) differences between homologous regions.

Similar to Wiedemann et al. (1999) we computed Pearson product-moment correlations between the anterior or posterior (right minus left) alpha asymmetry scores and measures of PTSD symptom severity (CAPS Total Score, PTSD dimensions: Reexperiencing, Avoidance, Numbing, and Hyperarousal), self-reported Depression (BDI), as well as PANAS-state NA and PA ratings. These correlations were conducted on an exploratory basis, so that two-tailed significances were reported in Table 4 and Table 6. Since the sample size is rather small for correlational analyses, we did not perform corrections for multiple testing in order to avoid that the analyses are substantially underpowered. Demographic and state-affect variables were assessed using analysis of variance (ANOVA) with Tukey post-hoc testing and Chi-Square tests.

3.1.3 Results

Baseline

Affective Ratings. Group by Gender ANOVAs were computed for negative (PANAS-NA) and positive (PANAS-PA) affect scores separately. For PANAS-NA scores this analysis revealed a significant effect for Group [$F(3,79) = 4.178, p < .01, \eta^2 = .137$]. Tukey multiple comparison tests indicated that PTSD patients reported significantly more negative affect than non-PTSD subjects ($p < .05$) and healthy controls ($p < .001$) but did not differ from the group with subsyndromal PTSD (see Table 2) . There was no significant difference between the three groups: non-PTSD, healthy controls, and subsyndromal PTSD (all $p > .27$).

For PANAS-PA scores there was a significant effect for Group [$F(3,79) = 4.44, p < .01, \eta^2 = .144$]. PTSD patients reported significantly less positive affect than non-PTSD participants ($p < .05$) and healthy controls ($p < .03$) but did not differ from the subsyndromal PTSD group ($p = .90$). The two control groups did not differ in baseline positive affect. There was a tendency for participants with subsyndromal PTSD to show less positive affect than the non-PTSD subjects ($p = .08$) but the positive affect of subsyndromal PTSD participants was

not lower than for healthy controls ($p = .14$). No main effects or interactions with Gender were revealed for baseline affect.

Table 2: Means, Standard Deviations, and Significance Tests for PANAS-State Scales of the Diagnostic Groups

	Healthy		Non-PTSD withSubsyndromal				PTSD		One-way	
	Controls		MVA		PTSD				ANOVA	
	M	SD	M	SD	M	SD	M	SD	F	p
PANAS-State Negative Affect										
Baseline	12.74	.86	13.43	2.29	14.33	2.24	16.23	4.79	5.99	<.001
Neutral Picture	12.26	.86	13.52	3.68	13.62	2.44	13.00	6.18	1.54	.21
Positive Picture	12.17	.83	12.24	0.77	13.19	2.52	12.68	1.73	1.82	.15
Negative Picture	21.17	8.85	19.76	7.41	20.19	7.65	22.95	9.14	0.63	.60
Trauma-related Picture	23.48	8.47	17.95	4.98	26.57	8.51	32.91	8.41	13.91	<.001
PANAS-State Positive Affect										
Baseline	36.52	9.26	37.24	7.01	31.43	8.15	29.77	6.31	4.88	.01
Neutral Picture	30.30	8.80	30.00	10.52	27.43	9.13	23.68	10.40	1.44	.24
Positive Picture	41.52	9.39	38.81	10.31	39.57	9.19	35.27	9.96	1.61	.20
Negative Picture	31.35	6.49	26.81	7.59	27.29	8.15	25.68	6.30	2.70	.06
Trauma-related Picture	29.48	4.80	26.62	6.14	24.10	3.82	22.95	7.80	10.19	<.001

PANAS = Positive and Negative Affect Schedule

Electrophysiology. The MANOVA conducted on baseline EEG alpha power (see Table 3 for EEG values) revealed a main effect for Baseline-Condition [$F(1,79) = 153.47, p < .001, \eta^2 = .660$] reflecting higher alpha power during the eyes closed condition. There were significant main effects for Region [$F(1,79) = 176.65, p < .001, \eta^2 = .660$] and a Region by Baseline-Condition interaction [$F(1,79) = 11.76, p < .01, \eta^2 = .130$]. Alpha power was higher at posterior sites. Furthermore, alpha activity was more reduced at posterior sites during the eyes open-condition in contrast to the eyes closed-condition. There was also a main effect for Hemisphere [$F(1,79) = 7.05, p < .05, \eta^2 = .082$] and a Hemisphere by Region by Baseline-Condition interaction [$F(1,79) = 7.39, p < .01, \eta^2 = .086$]. This reflects smaller alpha (greater activity) over left than right anterior regions in the eyes open condition compared to the eyes closed condition. However, there was no main effect for group or interaction with group. Furthermore, there were no significant interactions with gender of relevance for our hypotheses (interaction with group and hemisphere).

Table 3: Electroencephalograph (EEG) In Alpha Power values for Left and Right Anterior and Posterior Regions during Baseline

	Healthy Controls		Non-PTSD with MVA		Subsyndromal PTSD		PTSD									
	Left		Right		Left		Right									
	M	SD	M	SD	M	SD	M	SD								
Anterior Region	-1.17	.79	-1.17	.75	-1.68	1.06	-1.61	1.03	-1.73	.85	-1.66	.78	-1.46	.69	-1.41	.72
Posterior Region	-.69	.87	-.62	.82	-1.19	1.23	-1.09	1.20	-1.25	.95	-1.21	.87	-.93	.86	-.88	.86

Lower alpha scores indicate greater activity. Left = left hemisphere; Right = right hemisphere

Table 4: Correlations and Partial Correlations of Baseline EEG Alpha Asymmetry Scores (Right minus Left Hemisphere) for Anterior and Posterior Regions with Symptom Severity Measures and State Affect

	Anterior Asymmetry		Posterior Asymmetry	
Correlations				
CAPS Total Score ^a		.07		-.07
Reexperiencing ^a		.02		-.18
Avoidance ^a		-.01		-.01
Numbing ^a		.07		.01
Hyperarousal ^a		.12		-.03
BDI ^b		-.04		-.07
PANAS State NA ^c		.13		.11
PANAS State PA ^c		.08		.08
Partial Correlations (BDI as Covariate)				
CAPS Total Score ^d		.22		.01
Reexperiencing ^d		.09		-.15
Avoidance ^d		.03		.01
Numbing ^d		.18		.10
Hyperarousal ^d		.21		.07

CAPS = Clinician-Administered PTSD Scale, BDI = Beck Depression Inventory Depression, PANAS = Positive and Negative Affect Schedule. ^a N = 64, ^b N = 85, ^c N = 87, ^d N = 62

Correlational Analysis. We computed alpha asymmetry scores (right minus left) for the anterior and posterior regions based on baseline EEG alpha power (collapsed for eyes open and closed conditions). Positive correlations reflect relative increased left hemisphere activation. As can be seen in Table 4 there were no significant associations between trait and state measures and asymmetry scores for the baseline. BDI and PTSD severity (CAPS Total Score) were highly correlated ($r = .72$, $n = 62$, $p < .001$). It has been hypothesized that depression and anxious arousal may have opposite effects on brain asymmetry (Heller & Nitschke, 1998). We therefore computed partial correlations between anterior/posterior

asymmetry scores and PTSD symptoms using the BDI as covariate. Partial correlations between baseline asymmetry and symptoms of PTSD (ranging from -.15 to + .22) were not significant (see Table 4, bottom).

Stimulus phases

Affective Ratings. A repeated measures Group x Gender x Emotion-Condition (neutral, positive, negative, trauma-related) ANOVA was computed for PANAS-NA and PANAS-PA scores separately. For PANAS-NA scores this analysis revealed significant main effects for Group [$F(3,79) = 4.63, p < .01, \eta^2 = .149$], Emotion-Condition [$F(3,79) = 98.43, p < .001, \eta^2 = .555$] and a significant interaction Group x Emotion-Condition [$F(9,237) = 6.27, p < .001, \eta^2 = .192$]. Figure 1 shows an increase in the self-reported negative affect in response to the trauma-related picture compared to neutral and positive pictures. PTSD Patients showed the highest increase in negative affect in response to the traumatic picture. The group differences in the PANAS-NA ratings were not significant in post-hoc one-way ANOVAs for the neutral, positive, and negative picture (see Table 2). However, for the trauma-related picture there was a large group difference [$F(3,79) = 13.91, p < .001, \eta^2 = .334$] with PTSD patients reporting significantly more negative affect than non-PTSD subjects ($p < .001$), healthy controls ($p < .001$), and the subsyndromal PTSD group ($p < .05$). Furthermore, the subsyndromal PTSD group rated their mood after the trauma-related picture significantly more negative than non-PTSD subjects with MVA ($p < .01$) but not compared to healthy controls ($p = .56$) who showed a tendency of displaying more NA than non-PTSD subjects ($p = .09$).

For PANAS-PA scores this analysis revealed significant main effects for Group [$F(3,79) = 3.88, p < .05, \eta^2 = .124$] and Emotion-Condition [$F(3,79) = 70.31, p < .001, \eta^2 = .462$], but no significant interaction Group x Emotion-Condition ($p = .57$). The positive picture elicited more positive affect than the other stimulus types. Non-traumatized HC showed the most positive affect whereas PTSD patients showed the least. No main effects or interactions with Gender occurred for PANAS NA or PA.

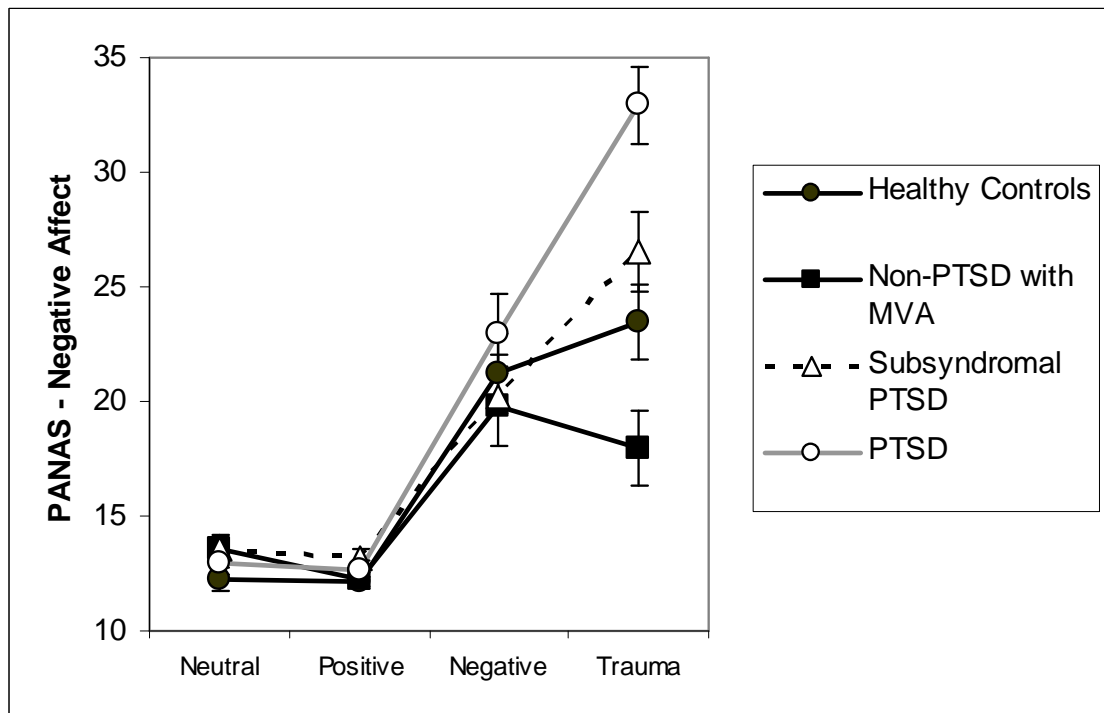


Figure 3. Mean state negative affect as assessed by the PANAS (Krohne et al., 1996) during picture presentation in healthy controls, non-PTSD controls with MVA, patients with subsyndromal PTSD and full PTSD. Error bars represent standard errors of the mean. PTSD = posttraumatic stress disorder; MVA = motor vehicle accident.

Electrophysiology. The MANOVA Group x Gender x Hemisphere x Region x Emotion Condition using EEG alpha power change scores (neutral minus emotion-condition) as dependent variables (see Table 5 for EEG values) resulted in a significant Group by Hemisphere by Emotion-Condition interaction [$F(6,158) = 2.19, p < .05, \eta^2 = .077$] and a Group by Gender by Hemisphere by Region by Emotion-Condition interaction [$F(6,158) = 2.27, p < .05, \eta^2 = .079$]. To further explore the group differences in alpha activity separate Group x Gender x Hemisphere x Region MANOVAs were computed for each condition. For the positive condition there were no significant main effects or interactions with Group (all $p > .22$). For the negative condition again no significant main effects or interactions with Group were revealed (all $p > .27$). However, as predicted for the trauma-related condition there was a significant Group x Hemisphere interaction [$F(3,56) = 9.55, p < .001, \eta^2 = .338$] and a Group by Gender by Hemisphere by Region interaction [$F(3,79) = 3.97, p < .05, \eta^2 = .131$]. The Group x Hemisphere interaction was significant for both anterior [$F(3,79) = 3.46, p < .05, \eta^2 = .116$] and posterior [$F(3,79) = 4.25, p < .01, \eta^2 = .116$] regions. Post-hoc simple-effects MANOVAs conducted for each group separately revealed for the anterior region marginally

significant hemisphere effects for the PTSD group [$F(1,21) = 3.23, p < .09, \eta^2 = .133$] and the subsyndromal PTSD group [$F(1,20) = 3.45, p < .08, \eta^2 = .147$] indicating greater relative right sided activation (see Figure 2). In contrast, the non-PTSD group showed the opposite pattern of increased relative left anterior activation [$F(1,20) = 11.18, p < .01, \eta^2 = .359$] which was not significant for the HC group [$F(1,22) = 2.37, p = .14$]. For the posterior region post-hoc simple-effects MANOVAs showed greater right than left activation in the PTSD group [simple hemisphere effect, $F(1,21) = 4.82, p < .05, \eta^2 = .187$] and the subsyndromal PTSD group [$F(1,20) = 6.15, p < .05, \eta^2 = .235$] and no significant hemispheric difference in the non-PTSD group [$F(1,20) = 2.42, p = .14$] and HC's [$F(1,22) = 0.00, p = .99$].

Table 5: EEG Alpha Power Change Scores (Neutral minus Emotion Condition) for Left and Right Anterior and Posterior Regions

Picture type and region	Healthy Controls		Non-PTSD with MVA		Subsyndromal PTSD		PTSD									
	Left		Right		Left		Right									
	M	SD	M	SD	M	SD	M	SD								
Positive																
Anterior Region	.234	.373	.238	.408	.09	.697	.092	.790	-.198	.371	-.182	.502	.121	.553	.059	.444
Posterior Region	.145	.344	.123	.354	.132	.799	.075	.691	-.098	.297	-.087	.455	.073	.467	.081	.354
Negative																
Anterior Region	.091	.378	.095	.414	.159	.531	.073	.431	.083	.510	-.013	.386	.023	.460	.047	.711
Posterior Region	-.007	.527	.053	.485	.190	.548	.174	.456	-.018	.418	.045	.347	-.021	.431	-.099	.352
Trauma-Related																
Anterior Region	.208	.350	.128	.302	.181	.402	.015	.334	.192	.450	.293	.469	.272	.617	.403	.430
Posterior Region	.184	.326	.183	.352	.198	.368	.101	.256	.041	.412	.215	.355	.197	.499	.315	.369

Since EEG alpha power is inversely related to activity, positive change score values (neutral minus emotion condition) denote increased activation during exposure to the positive, negative or trauma-related picture. Left = left hemisphere; Right = right hemisphere.

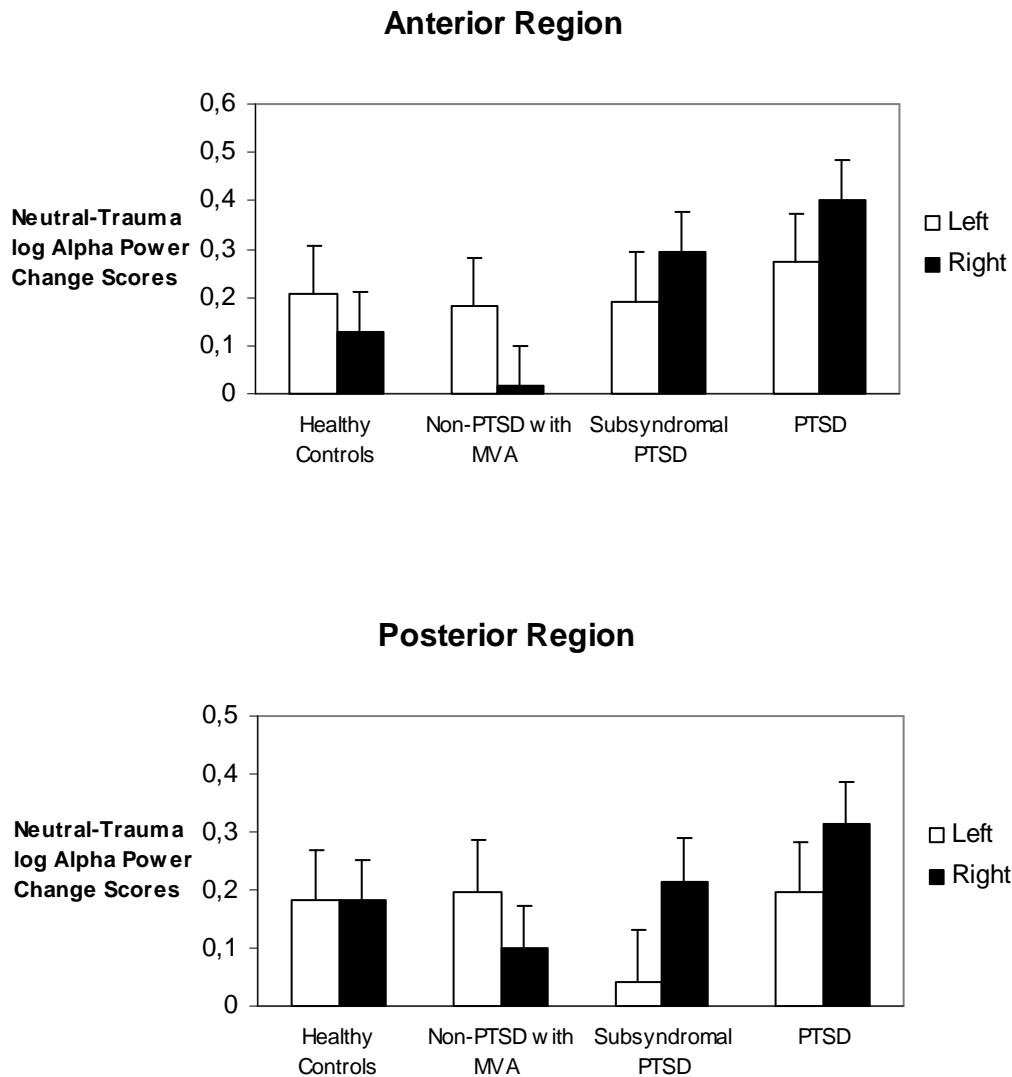


Figure 4. EEG alpha power change scores (neutral minus trauma condition) for the left and right anterior (upper panel) and posterior regions (lower panel) in healthy controls, non-PTSD controls with MVA, patients with subsyndromal PTSD and full PTSD. Since EEG alpha power is inversely related to activity positive change score values denote increased activation during exposure to the trauma-related picture. Left = left hemisphere; Right = right hemisphere. Error bars represent standard errors of the mean.

To explore gender differences in brain electrical asymmetry during the trauma-related condition we computed separate MANOVAs for anterior and posterior regions. There was no Group by Gender by Hemisphere interaction for the anterior region ($p = .70$) but for the posterior region [$F(3,79) = 3.37, p < .03, \eta^2 = .113$]. Follow-up Gender by Hemisphere MANOVAs conducted for each diagnostic group separately revealed that only for healthy controls there was a significant Gender by Hemisphere interaction [$F(1,21) = 12.92, p < .01,$

$\eta^2 = .381$] but not for the three MVA groups (all $p > .19$). Healthy women showed a pattern of right-sided posterior activation in contrast to men who showed the opposite pattern¹To rule out the possibility that gender is confounding our results we repeated the analyses for the trauma-related condition using female participants only ($n = 60$). Again, there was a significant Group x Hemisphere interaction [$F(3,56) = 9.55, p < .001, \eta^2 = .338$], whereas the Group x Hemisphere x Region interaction failed to reach significance [$F(3,56) = 2.15, p = .11$]. For the anterior region there was a significant Group by Hemisphere interaction [$F(3,56) = 6.25, p < .001, \eta^2 = .251$]. Post-hoc simple-effects MANOVAs conducted for each group separately revealed greater right than left anterior activation for women with full PTSD or subsyndromal PTSD (both $p < .05$) and greater left than right anterior activation for the non-PTSD ($p < .05$) and the HC group ($p < .10$). For the posterior region there was a significant Group by Hemisphere interaction [$F(3,56) = 6.32, p < .001, \eta^2 = .253$] indicating greater right than left hemisphere activation for PTSD, subsyndromal PTSD, and HC groups (simple hemisphere effects, all $p < .05$) and greater relative left hemisphere activation in the non-PTSD group ($p < .05$).

Correlational Analysis. We computed alpha asymmetry scores (right minus left) for the anterior and posterior regions based on EEG alpha power change scores (neutral minus emotion condition). Positive correlations reflect relative increased right hemisphere activation. As can be seen in Table 6 significant correlations were found only for the trauma-related condition between *anterior asymmetry* and overall PTSD severity (CAPS Total Score) as well as the three PTSD dimensions Reexperiencing, Avoidance, and Hyperarousal as well as the BDI. Furthermore, we observed positive associations of *posterior asymmetry* for the trauma-related condition with PTSD severity (CAPS Total Score), Reexperiencing, and Hyperarousal. In addition, only for the trauma-related condition there were significant positive correlations between increased negative affect (PANAS-State NA) and *anterior asymmetry* as well as *posterior asymmetry*. Higher NA was associated with greater relative right hemisphere activation during the trauma-related condition. Finally, PANAS-State PA was negatively related to *posterior asymmetry*.

To assess whether the relationship of PTSD symptoms with relative right hemisphere activation during the trauma-related condition was specific to the PTSD symptoms, we computed partial correlation coefficients partialing out BDI depression (see bottom of Table 6). Again, for the trauma-related condition there were significant partial correlations between *anterior asymmetry* and overall PTSD severity as well as the PTSD dimensions

Reexperiencing. *Posterior asymmetry* was associated with overall PTSD severity, Reexperiencing, and Hyperarousal even when controlling for BDI.

Table 6: Correlations and Partial Correlations of EEG Asymmetry (Right minus Left Hemisphere) based on Alpha Power Change Scores (Neutral minus Emotion Condition) for Anterior and Posterior Regions with Symptom Severity Measures and State Affect

	Positive Picture		Negative Picture		Trauma-Related Picture	
	Anterior	Posterior	Anterior	Posterior	Anterior	Posterior
	Asymmetry	Asymmetry	Asymmetry	Asymmetry	Asymmetry	Asymmetry
Correlations						
CAPS Total Score ^a	.09	.21	.05	.18	.44**	.37**
Reexperiencing ^a	.06	.24	.04	.22	.48**	.47**
Avoidance ^a	.15	.03	.03	.00	.34*	.19
Numbing ^a	.09	.13	.07	.11	.19	.11
Hyperarousal ^a	.02	.21	.03	.16	.41**	.38**
BDI ^b	.10	.14	.07	.16	.29**	.15
PANAS State NA ^c	.16	-.08	-.12	-.01	.35**	.26**
PANAS State PA ^c	-.08	.00	.17	.08	-.15	-.24*
Partial Correlations (BDI as Covariate)						
CAPS Total Score ^d	-.08	.04	-.05	.04	.28*	.35**
Reexperiencing ^d	-.03	.13	-.02	.17	.38**	.46**
Avoidance ^d	.12	-.07	-.04	-.11	.22	.15
Numbing ^d	-.05	-.04	-.02	-.04	-.07	-.04
Hyperarousal ^d	-.08	.04	-.08	.02	.25	.35**

All tests are two-tailed. * $p < .05$; ** $p < .01$; ^a $N = 64$, ^b $N = 85$, ^c $N = 87$, ^d $N = 62$

The role of concussion and loss of consciousness

In order to address the question whether reversible neurological trauma in our MVA sample could have affected either baseline EEG or EEG responses to the experimental stimuli we repeated above analyses comparing the four groups using only MVA victims without concussion and loss of consciousness. The findings were essentially the same as for the total samples. Again only for the trauma-related condition there was a significant Group by Hemisphere interaction [$F(3,52) = 3.54$, $p < .05$, $\eta^2 = .169$].

The role of comorbid depression

It was important to rule out possible effects related to the presence of comorbid depression. Therefore, we collapsed subsyndromal PTSD patients with comorbid MDD ($n = 4$) and PTSD

patients with MDD (n = 9) or dysthymia (n = 2) to one group (subsyndromal/full PTSD + DEP, n = 15). PTSD patients and the subsyndromal PTSD without comorbid depression were also collapsed to one group (subsyndromal/full PTSD - DEP, n = 28). Using the group variable (HC, non-PTSD controls with MVA, subsyndromal/full PTSD - DEP, subsyndromal/full PTSD + DEP) we repeated above analyses for baseline and emotion conditions. Again only for the trauma-related condition there was a significant Group by Hemisphere interaction [$F(3,83) = 7.48, p < .001, \eta^2 = .213$]. To test directly the hypotheses that PTSD groups with and without depression are characterized by distinct hemispheric asymmetries, the two groups were compared. This resulted in no statistical difference in brain asymmetry as revealed by non significant Group by Hemisphere or Group by Hemisphere by Region interactions (all $p > .47$). Even when the four PTSD patients with lifetime but not current major depression were included in the PTSD + MD group the results did not change.

Other frequency bands

We computed power for the three other traditional frequency bands: delta (1-4 Hz), theta (4-8 Hz), and beta (13-30 Hz). We repeated analyses for baseline and emotion conditions using the same MANOVAs as for the alpha band. Since we had no specific hypotheses for effects in these three bands we reduced the likelihood of a type I error by means of Bonferroni adjustment to an alpha of $p < .017 (.05/3)$. There was no significant interaction or main effect with Group (all $p > .06$). Especially the key interactions Group by Hemisphere by Condition and Group by Hemisphere by Region by Condition were not significant (all $p > .16$).

3.1.4 Discussion

This study examined hemispheric asymmetries among MVA survivors with PTSD, subsyndromal PTSD, and without PTSD as well as non-exposed healthy controls during baseline and in response to neutral, positive, negative, and trauma-related pictures. In accordance with our hypothesis, both PTSD and subsyndromal PTSD patients displayed a pattern of increased right-sided activation in anterior and posterior regions during exposure to a trauma-related picture as compared to non-PTSD and healthy controls. This pattern of brain asymmetry in PTSD and subsyndromal PTSD was accompanied by increased negative affect. No significant group by hemisphere interactions were observed for the other emotional conditions and the resting baseline condition. Correlational analysis revealed that only for the trauma-related condition relative right hemispheric anterior and posterior activation was

associated with greater total PTSD severity and PTSD dimensions Reexperiencing, Avoidance (only for anterior asymmetry), and Hyperarousal. Furthermore, most of the correlations remained significant after controlling for BDI-depression. The pattern of right hemisphere activation during exposure to the trauma-related picture might in part be explained by increased negative affect given the positive association of brain asymmetry and NA ratings. Finally, we ruled out that our results were due to reversible accident-related neurological trauma.

Contrary to our hypothesis, we observed no group differences in EEG alpha activity during the baseline condition although there were group differences in negative affect during this period. However, the absolute differences in baseline affect were rather small. This finding was unexpected, because previous research (Metzger et al., 2004) had led us to anticipate that posterior baseline asymmetry is associated with PTSD Hyperarousal. However, our results are in accordance with studies showing that PTSD patients after severe MVA display no heightened baseline psychophysiologic activity (e.g. heart rate) but increased psychophysiologic responsiveness to trauma-related stimuli (Blanchard, Hickling, Buckley et al., 1996; Blanchard, Hickling, Taylor, & Loos, 1994). Our results indicate that MVA-related PTSD is not necessarily related to a trait asymmetry.

The pattern of increased right anterior activation during the trauma-related condition in persons with PTSD and subsyndromal PTSD was similar to that previously reported during the presentation of anxiety-provoking stimuli in social phobics (Davidson, Marshall et al., 2000), panic patients (Wiedemann et al., 1999), and Vietnam veterans with PTSD (McCaffrey et al., 1993). It is in accordance with Positron Emission Tomography (PET) findings in PTSD (Rauch et al., 1996) and PTSD among other anxiety disorders (Rauch et al., 1997) reporting patterns of asymmetrical brain activation. The results support the model of Davidson (1995) in which right anterior activation is associated with the activation of an avoidance/withdrawal system. The findings are also in accordance with the model of Heller and colleagues (eg. Heller & Nitschke, 1998), in which it is assumed that negatively valenced emotions should be associated with relative right anterior activation. Our findings of increased relative right posterior activation in PTSD and subsyndromal PTSD is consistent with recent studies reporting right posterior activation during anxiety provoking situations in anxious participants (Davidson, Marshall et al., 2000; Heller et al., 1997). It has been hypothesized that right posterior activation is associated with anxious arousal in contrast to anxious apprehension which should be associated with increased left anterior activation (Heller et al., 1997). This

underlines that patients with full and subsyndromal PTSD may not be characterized by anxious apprehension but rather by anxious arousal when exposed to trauma-related stimuli. If the present results can be replicated and generalized to other trauma populations, they would indicate that EEG alpha asymmetry may be used to discriminate different types of pathologic anxiety conditions. Recent functional neuroimaging studies showed that emotionally laden visual stimuli elicit increased activation in posterior cortical regions (Lane, Chua, & Dolan, 1999; Lang et al., 1998). Nitschke, Heller, and Miller (2000) proposed a right hemisphere system that is involved in visual attention, orientation, and response to threat associated with anxiety. This could be an important component of a system mediating symptoms of PTSD like increased hypervigilance and physiological reactivity to traumatic cues.

The association between the PTSD dimension Reexperiencing with greater relative right hemisphere activation during exposure to the trauma-related picture indicate a link to maladaptive information processing and memory for traumatic events. Cognitive theories of PTSD (Brewin et al., 1996; Ehlers & Clark, 2000) propose that reexperiencing aspects of traumatic events are very vivid, mostly visual and emotional. These trauma memories are very different from recall of ordinary autobiographical memories in which sensory elements are integrated into a personal narrative and which seems to be primarily dependent on the left hemisphere (Maguire, 2001). However, further research is needed to explore the possible mechanisms underpinning the association of brain asymmetry and specific symptoms of PTSD.

The pattern of brain asymmetry during exposure to trauma-related material was similar between PTSD and subsyndromal PTSD patients. This was expected since persons with subsyndromal and full PTSD displayed comparable symptom severity in PTSD dimensions Reexperiencing, Avoidance, and to a lesser degree Hyperarousal. In contrast, psychological Numbing, the dimension in which there was a great difference between persons with subsyndromal and full PTSD, was not significantly related to brain asymmetry. However, it is worth noting that the relative right posterior activation in subsyndromal PTSD group is driven by a decrease in left posterior activity. Our results warrant further research on brain mechanisms related to subsyndromal PTSD since these patients may suffer chronically from PTSD symptoms (e.g. Blanchard, Hickling, Barton et al., 1996).

The opposite pattern of relative left hemisphere activation during exposure to the trauma-related picture (accompanied with the lowest negative affect) was observed in MVA victims who have recovered from trauma (non-PTSD). This might reflect more adaptive

tendencies to process trauma-related information in an approach-related (vs. avoidance), low anxious-aroused and verbally integrated manner. Relative left frontal hemisphere activation has been proposed to be associated with a self enhancing regulatory style inhibiting negative affective responses (Tomarken & Davidson, 1994). The question whether the pattern of brain asymmetry in non-PTSDs with MVA is related to a specific type of coping should be explored in further studies.

Non-traumatized healthy controls displayed a pattern of more symmetrical brain activation. This group reacted with more negative affect to the trauma-related picture than MVA-non-PTSD controls. Furthermore, only in healthy controls posterior hemispheric asymmetry in response to the trauma-related picture varied with gender. Healthy women showed a pattern of relative right posterior activation similar to that of persons with PTSD and subsyndromal PTSD in contrast to men who showed the opposite pattern in the absence of gender differences in affect ratings. This finding was not predicted and we do not have a clear explanation for it. However, this gender effect in HC's is consistent with a prior report on healthy subjects indicating gender differences in posterior asymmetry in response to emotional tasks in the absence of sex differences in subjective ratings (Davidson, Schwartz, Pugash, & Bromfield, 1976). However, it has to be mentioned that our analysis of gender was clearly exploratory given the low proportion of males in our sample and especially the PTSD group. Recent research has shown that gender might be an important variable for the understanding of associations between brain asymmetry with coping (Kline et al., 1998) and depression (Miller et al., 2002). Therefore, future studies of the potential influence of gender differences on brain asymmetry are clearly warranted.

Post-hoc analyses comparing groups with and without comorbid depression showed that the EEG alpha asymmetry during baseline and other emotion conditions were not modulated by comorbid depression. When statistically controlling for symptoms of BDI-depression by means of partial correlations most of the observed relations between PTSD symptoms and brain asymmetry for the trauma-related condition remained significant. This does not support the hypothesis that comorbid depression should attenuate right posterior activation (Heller & Nitschke, 1998). However, our results are in accordance with research showing that depression with comorbid anxiety differs from depression without anxiety in measures of EEG asymmetry (Bruder et al., 1997; Kentgen et al., 2000).

Some remarks have to be made concerning our methodology. In the current study we used pictures. The use of trauma-related pictures has several advantages over other techniques

for mood induction in PTSD patients. Unlike personalized scripts, pictures can be presented in an identical fashion to all subjects. Furthermore, pictures have a greater resemblance to traumatic triggers that patients encounter in their environment. Even if standardized, stimuli like pictures with only vague physical similarity to the traumatic situation can serve as triggers for reexperiencing symptoms (poor stimulus discrimination) (Ehlers & Clark, 2000). However, the use of only one stimulus per emotion category may impair generalizability of our results. Furthermore, our assessment of negative affect (PANAS) does not allow us to conclude what discrete emotion or affective state was elicited by the trauma-related picture. Given the relatively low association between negative affect and EEG alpha asymmetry during the trauma-related condition an increase in general negative affect alone is unlikely to account for increased right-sided activity. Future studies are needed to index what cognitive or affective processes are linked to hemispheric EEG activation in PTSD.

A limitation of the current study is the poor spatial resolution of scalp-recorded electrophysiology. Studies using neuroimaging techniques with better spatial resolution are needed to confirm our findings. However, the EEG can provide useful information about hemispheric differences in broad regions of the cortex and has the advantage of being relatively inexpensive and completely noninvasive making it ideally suitable for studies with large samples especially patient populations.

In the current study we included only traumatized persons with MVA. Therefore, the results may not be generalizable to other trauma populations. The differences between the two control groups in affective and brain asymmetry responses to trauma-related stimuli underline the need to include non-traumatized controls in PTSD research.

In summary, persons with PTSD and subsyndromal PTSD demonstrated increased right-sided anterior and posterior activation only during exposure to a trauma-related picture but not during baseline and other emotion-conditions. These findings suggest that PTSD may be linked to a context-dependent trauma-specific alteration in hemispheric processing which is associated with anxious arousal and symptoms of PTSD.

3.2 Study II: Changes in brain electrical activity after cognitive behavioral therapy for posttraumatic stress disorder in patients injured in motor vehicle accidents*

3.2.1 Introduction

Models of brain asymmetry and emotion proposed that greater left frontal activation is associated with approach motivation, emotion, and behavior, whereas greater right frontal cortical activation is associated with withdrawal motivation, emotion, and behavior (Coan & Allen, 2003b; Davidson, 1998b; Harmon-Jones & Allen, 1998; Sutton & Davidson, 1997). Evidence for these assumptions comes from research investigating brain asymmetries in the alpha band of the electroencephalogram (EEG) as an inverse index of brain activation (for review see Coan & Allen, 2004). According to these hypotheses, studies investigating EEG asymmetries in anxiety disorders reported increased right anterior activation during symptom provocation in panic patients (Wiedemann et al., 1999), social phobics (Davidson, Marshall et al., 2000), and Vietnam veterans with PTSD (McCaffrey et al., 1993). Recently, Metzger et al (2004) reported an association of PTSD arousal symptoms with increased relative right parietal activity during a resting condition in a sample of female Vietnam War nurse veterans. This finding was consistent with the suggestion of Heller and colleagues (Heller et al., 1997; Nitschke et al., 1999) who proposed that anxious arousal is related to increased right posterior activation.

In a recent study we examined brain electrical activity in motor vehicle accident (MVA) survivors with posttraumatic stress disorder (PTSD), subsyndromal PTSD, and without PTSD as well as healthy controls without severe MVA during baseline and during confrontation to neutral, positive, negative, and trauma-related pictures (Rabe, Beauducel, Zollner, Maercker, & Karl, 2006). We found that participants with PTSD and subsyndromal PTSD showed a pattern of enhanced right anterior and posterior activation in response to the trauma-related accident picture. This trauma-specific increase in relative right hemisphere activation was correlated with increased negative affect and PTSD symptoms. The findings of increased right hemisphere activation in PTSD were in accordance with neuroimaging

* This study is already published (Rabe, Zoellner, Beauducel, Maercker, & Karl, 2008). Reprint of content with permission of Wolters Kluwer Health.

findings in PTSD (Pagani et al., 2005; Rauch et al., 1996) and PTSD among other anxiety disorders (Rauch et al., 1997).

The aim of the present study was to examine whether the pattern of increased right hemisphere asymmetry observed in MVA survivors with chronic PTSD and subsyndromal PTSD will change due to treatment with cognitive-behavioral therapy (CBT). There has been relatively little research on changes of brain asymmetry due to therapeutic interventions. In a recent study, Davidson et al (2003) examined changes in brain electrical asymmetry and immune function following a meditation program. They found that the meditation group showed significant larger increases in left-sided anterior activation (during baseline and positive, negative emotion induction) compared to a wait-list group. The increase in relative left anterior brain activity was associated with an increase in antibody titers to an influenza vaccine received immediately after the training program. In contrast, baseline anterior asymmetry has been found to be stable and unrelated to changes in clinical status due to bright light exposure in seasonal affective disorder (Allen et al., 1993), acupuncture treatment for major depression (Allen et al., 2004). Furthermore, Deldin and Chiu (Deldin & Chiu, 2005) showed that baseline frontal asymmetry is stable in individuals with major depression before and after a cognitive intervention but may predict treatment response.

There are few neuroimaging studies investigating brain changes due to psychotherapy (for review see Roffman et al., 2005). Functional changes of brain activity after successful psychological treatment have been reported for depression (Goldapple et al., 2004) and obsessive compulsive disorder (Schwartz, Stoessel, Baxter, Martin, & Phelps, 1996). There are limited data available showing changes in regional brain activity due to cognitive-behavioral therapy in anxiety disorders as social phobia (Furmark et al., 2002), panic disorder (Prasko et al., 2004), and simple phobia (Paquette et al., 2003). Regarding PTSD there is only one case study of a man who experienced violence in childhood (Levin et al., 1999). Brain activation during symptom provocation using script-driven imagery was measured before and after three sessions of eye movement desensitization and reprocessing (EMDR) (with parallel antidepressant treatment). At post-assessment two areas showed an increased activation: the anterior cingulate gyrus and the left frontal lobe.

CBT is an effective psychotherapeutic approach for reducing the symptoms of PTSD (Bradley et al., 2005). It is designed to alter dysfunctional affective processing related to PTSD such as behavioral and emotional avoidance, intrusive recollections and hyperarousal. Several mechanisms like habituation, change of interpretations of the traumatic event, and a

change of maladaptive coping strategies have been suggested to explain the therapeutic effects. To our knowledge there is no study that investigated the neural correlates of change due to cognitive-behavioral therapy in PTSD. Therefore, we measured EEG activity before and after CBT (in comparison to an assessment-only Wait-list condition) as part of a previously completed controlled, randomized treatment trial for MVA-related PTSD (Maercker et al., 2006). Since CBT leads to a decrease of PTSD symptoms and anxiety we hypothesized that participants receiving CBT would exhibit a greater decrease in right anterior and posterior activation during exposure to a trauma-related accident picture compared to the Wait-list group.

3.2.2 Methods

Participant population

As described elsewhere (Maercker et al., 2006) 42 participants with PTSD or subsyndromal PTSD completed the treatment trial and pre- and post-assessments. They were recruited through self-referral local media coverage and advertising. All participants received a comprehensive description of the study and provided written informed consent at the initial diagnostic assessment. The protocol was approved by the ethics board of the Dresden University of Technology.

Current diagnosis of PTSD or subsyndromal PTSD were determined by a German version (Schnyder & Moergeli, 2002) of the Clinician Administered PTSD Scale (CAPS-DX or CAPS-1, Blake et al., 1995). This scale represents a standardized interview that allows generating categorical diagnosis of current and lifetime PTSD as well as a total score obtained by summing the ratings of frequency and severity of each of the 17 PTSD symptoms (CAPS Score) according to the DSM-IV (*Diagnostic and Statistical Manual of Mental Disorders*, 1994). Subjects receiving PTSD diagnosis were required to meet all three symptom clusters (B through D) for PTSD according to DSM-IV criteria. Diagnosis of subsyndromal PTSD (sub-PTSD) was given if patients met the DSM-IV criteria B (Intrusion) and either Criterion C (Avoidance/Numbing) or Criterion D (Hyperarousal) following the most prominent definition of subsyndromal PTSD proposed by Blanchard and colleagues (e.g., Blanchard, Hickling, Taylor, & Loos, 1995). Previous research has shown that the diagnosis of subsyndromal PTSD has clinical relevance and is associated with significant distress (Schuetzwohl & Maercker, 1999; Zlotnick, Franklin, & Zimmerman, 2002).

Exclusion criteria for the current investigation were (1) a history of neurological problems like epilepsy, brain surgery, brain damage or severe head injury during the accident, (2) current alcohol and/or substance abuse or dependence, (3) current or past schizophrenic, bipolar, or psychotic disorder, and (4) any current treatment or psychotropic medication for at least 1 month before testing. We did not exclude participants with reversible neurological trauma (concussion and loss of consciousness). All participants were right-handed as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). From 42 participants of the treatment trial, 5 were excluded for the current study because they did not meet the inclusion criterion to be off psychotropic medication during the pre-assessment. Two participants were excluded because of EEG recording errors during the pre-assessment. This resulted in a final sample of 35 patients, 17 in the CBT group (10 PTSD, 7 sub-PTSD), 18 in the Wait-list group (7 PTSD, 11 sub-PTSD). The CBT group and the Wait-list group did not differ significantly in the proportion of full PTSD to subsyndromal PTSD [$\chi^2(1) = 1.39$; $p = .24$]. EEG pre-assessment data of these participants have been part of a previous report on differences between persons with and without PTSD (Rabe, Beauducel et al., 2006).

The Structured Clinical Interview for the DSM-IV (SCID-I) (First et al., 1996; Wittchen et al., 1997) evaluated the presence of concurrent and lifetime DSM-IV Axis I disorders. Comorbid diagnoses in the CBT group were lifetime but not current major depression (MDD) ($n = 3$), current MDD ($n = 6$), panic disorder without agoraphobia ($n = 1$), agoraphobia without panic disorder ($n = 1$), social phobia ($n = 3$), specific phobia ($n = 1$), obsessive compulsive disorder ($n = 1$), and lifetime generalized anxiety disorder ($n = 1$). Additional diagnoses in the Wait-list group were lifetime but not current MDD ($n = 3$), current MDD ($n = 3$), panic disorder without agoraphobia ($n = 1$), social phobia ($n = 2$), and specific phobia ($n = 3$).

Treatment trial and instruments

A full description of the randomized, controlled treatment trial has been submitted recently (Maercker et al., 2006). The study was conducted at the University of Technology Dresden, Germany, from April 2002 to February 2005. After the initial assessment, patients were matched into dyads based on CAPS Score, age, and comorbidity and then randomly assigned to one of two conditions: (1) CBT ($n = 17$, 15 females) or (2) Wait-list ($n = 18$, 10 females). The CBT was conducted according to a German adaptation and extension of the CBT manual of Hickling & Blanchard (1997) and has been published previously (Zöllner, Karl, Maercker,

Hickling, & Blanchard, 2005). The CBT program consisted of 8–12 weekly sessions each about 1.5 hours. It includes standard CBT techniques for treatment of PTSD: writing exposure, prolonged imaginal exposure, in-vivo exposure, cognitive restructuring, and relaxation training. Additionally, it includes new sections for treatment of guilt or anger and a section on facilitation of posttraumatic growth. The Wait-list control individuals were reassessed after 3 months and received CBT if they were still interested in treatment.

At post-assessment PTSD symptoms were assessed using a German version of the CAPS specifically designed for reassessments (CAPS-2) (Blake et al., 1990) asking for severity of PTSD symptoms during the last week. Several self-report psychological questionnaires were also utilized including a German version (Hautzinger et al., 1994) of the Beck Depression Inventory (BDI) (Beck & Steer, 1987) for assessment of presence and severity of depressive symptoms. The Impact of Event Scale-Revised (IES-R; German version: Maercker & Schützwohl, 1998) (Maercker & Schuetzwohl, 1998) asked for self-reported PTSD symptoms of intrusions, avoidance, and hyperarousal. The German version (Laux et al., 1981) of the State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1970) scored for both state anxiety and trait anxiety. State and trait affect were assessed by an extended German version (Krohne et al., 1996) of the Positive and Negative Affect Schedule (PANAS) (Watson et al., 1988).

Electrophysiological recording procedure and analysis

The procedure for measurement of EEG activity during baseline and mood induction was described in our previous report (Rabe, Beauducel et al., 2006) and was identical between pre- and post-assessments. Measures of electroencephalographic activity were obtained before assignment to each of the two treatment groups and then after completion of CBT (or after 3 months for Wait-list controls). EEG was recorded during an 8 minutes baseline condition as described elsewhere (Tomarken, Davidson, Wheeler, & Kinney, 1992). This was followed by a presentation of 4 pictures, 1 minute each (neutral, positive, negative, trauma-related). The accident-picture was a photograph from a crashed car lying on the roof. The positive (two bunnies), negative (a barking dog), and neutral (spoon) pictures were taken from the International Affective Picture System (IAPS) (Lang et al., 1988). Following baseline and after viewing each picture, subjects rated their actual mood with the PANAS-state questionnaire.

EEG was recorded from 28 scalp placements (Fp1, Fp2, F7, F3, Fz, F4, F8, Fc5, Fc1, Fc2, Fc6, T7, C3, Cz, C4, T8, Cp5, Cp1, Cp2, Cp6, P7, P3, Pz, P4, P8, POz, O1, O2)

according to the extended 10-20 system (Pivik et al., 1993) using a stretchable electro cap (FMS, Falk Minow Services, Munich, Germany). Moreover, we recorded EEG activity at linked mastoid positions (A1, A2). All sites were online referenced to a computer averaged F3/F4 reference and grounded at AFz. Impedances were maintained below 5 k Ω and within 500 Ω at homologous sites. The EEG signal was recorded by a Nihon Kohden amplifier (NeuroFileII system), filtered with a time constant of 10 s and a high frequency cut-off (300 Hz) and digitized online at 1024 Hz and stored at 256 Hz. A linked-mastoids reference was rederived offline. Before further data processing, EEG artifacts (eye blinks and muscle artifacts) were removed by applying independent component analysis (ICA) (Jung et al., 2000) to the EEG segments of interest. Prior to artifact screening, an offline bandpass filter (1 to 30 Hz) was applied. Continuous EEG data were divided offline in 4 s epochs (50 % overlap) and again visually inspected for artifacts. All epochs free of artifacts were subjected to a fast Fourier transformation (FFT) using a Hamming window over the distal 50% of each epoch. By averaging segments, estimates of spectral power (μV^2) were derived for 0.25 Hz bins, averaged between 8-13 Hz, and normalized (natural log) to obtain ln power density (ln $\mu\text{V}^2/\text{Hz}$) in the alpha band. Alpha power is considered to be inversely related to cortical activity, with decreases in alpha power reflecting increases in activation (Cook, O'Hara, Uijtdehaage, Mandelkern, & Leuchter, 1998; Davidson, Jackson, & Larson, 2000).

In order to examine the emotion-induced activation relative to the neutral condition we computed neutral-minus-emotion-condition change scores by subtracting alpha activity during the three emotional conditions (positive, negative, trauma-related) from that of the neutral condition. Since a decrease in alpha power is inversely related to activity, positive change scores indicate greater activation during emotion compared to neutral condition. All reported effects are based upon these change scores. This approach has the advantage of controlling individual differences in the total amount of recorded alpha power e.g. produced by individual differences in skull thickness or occasion specific fluctuations. Furthermore, it allows examining changes in brain activation within one hemisphere instead of only comparing asymmetry scores (right minus left). Similarly to our previous report we assessed alpha activity in four quadrants of the scalp. Therefore we averaged electrode sites within left anterior (F3, F7, T7), right anterior (F4, F8, T8), left posterior (Cp5, P3, P7) and right posterior (Cp6, P4, P8) regions. This has the advantage of reducing the amount of data and according to the Spearman-Brown prophecy formula it increases reliability of anterior and posterior brain asymmetry measures.

Statistical analyses. In this report we examined the changes in brain electrical activation during viewing the trauma-related accident picture, since this was the only condition previously shown to discriminate symptomatic (PTSD, subsyndromal PTSD) and non-symptomatic MVA victims and non-MVA controls (Rabe, Beauducel et al., 2006). The statistical analysis focused on the interactions between Treatment-Group (CBT/Wait-list) and Time (Pre, Post). Repeated-measures multivariate analyses of variance (MANOVAs) were computed for anterior and posterior regions. Follow-up MANOVAs were performed for each group separately to examine changes in hemispheric activity.

3.2.3 Results

Pretreatment evaluation

CBT and Wait-list groups did not differ in age (CBT: mean = 38.65, sd = 11.47; Wait-list: mean = 41.89, sd = 11.03), and time since accident in months (CBT: mean = 74.18, sd = 114.61; Wait-list: mean = 41.39, sd = 32.77). There were no differences between groups in PTSD severity (CAPS Score) and questionnaire data (all $t < 0.89$, $ps > .34$) (see Table 7).

Table 7: Pre- and Post-treatment Values for Symptom Severity Measures and State Negative Affect for the Trauma-related Picture

Characteristics	CBT (N=17)		Wait-list (N=18)		Interaction	
	PRE	POST	PRE	POST	Group x Time	p
	M (SD)	M (SD)	M (SD)	M (SD)		
CAPS Score	46.94 (16.13)	15.24 (12.99)	41.39 (17.45)	34.72 (22.14)	F(1,33) = 25.32	< .001
IES-R	59.44 (14.43) ^a	23.94 (18.80)	57.28 (17.50)	49.72 (24.30)	F(1,32) = 26.54	< .001
BDI	16.44 (10.72) ^a	8.00 (6.60)	15.67 (8.90)	13.11 (10.32)	F(1,32) = 5.12	.03
STAI-Trait	48.81 (10.62) ^a	38.44 (9.39)	49.17 (12.51)	46.22 (13.52)	F(1,32) = 6.77	.01
Trait-NA	31.19 (7.31) ^a	24.69 (7.67)	27.35 (10.01) ^b	26.53 (10.33)	F(1,31) = 4.63	.04
State-NA *	28.94 (9.58)	22.71 (8.87)	29.72 (9.81)	27.17 (9.45)	F(1,33) = 1.78	.19

CBT = Cognitive Behavioral Therapy, CAPS = Clinician-Administered PTSD Scale, IES-R = Impact of Event Scale-Revised, BDI = Beck Depression Inventory Depression, STAI-Trait = State-Trait Anxiety Inventory - Trait Scale, Trait-NA = Trait Negative Affect assessed with the Positive and Negative Affect Schedule (PANAS), State-NA = State Negative Affect assessed with the PANAS. ^a N = 16, ^b N = 17; * State-NA for the accident picture

Treatment outcome measures

For the assessment of differences in treatment outcome we calculated a two-way repeated measures MANOVA on the CAPS Score with Time (Pre, Post) as within-subject factor and Treatment-Group (CBT, Wait-list) as between-subject-factor. This analysis revealed a significant interaction of Group x Time [$F(1,33) = 25.32, p < .001, \eta^2 = .434$] indicating a greater decrease in PTSD severity in the CBT group. Furthermore, as can be seen in Table 7, there were significant Group x Time interactions for self-report measures of PTSD severity (IES-R), depression (BDI), anxiety (STAI), and trait negative affect (PANAS). There was no significant Group x Time interaction for ratings of state negative affect (PANAS) during exposure to the accident picture [$F(1,33) = 1.78, p = .19$]. Since we a priori predicted a decrease in negative affect in the CBT group we examined the change over time for each group separately. There was a significant reduction in negative affect (PANAS) in the CBT group [$t(16) = 3.49, p = .003$] but not for Wait-list participants [$t(17) = 1.23, p = .24$].

Electrophysiology

Based on our previous finding of increased right anterior and posterior activation during exposure to a trauma-related picture in PTSD and subsyndromal PTSD subjects, we predicted a greater decrease in right hemisphere activation in patients receiving CBT. We computed a repeated measures MANOVA with Treatment-Group x Time x Hemisphere on alpha power change scores (neutral-trauma-related) for the anterior and posterior regions separately¹. For the anterior region this analysis revealed a marginally significant Time x Hemisphere interaction [$F(1,33) = 3.65, p = .06, \eta^2 = .100$] and a trend for the predicted Treatment-Group x Time x Hemisphere interaction [$F(1,33) = 3.49, p = .07, \eta^2 = .096$]². As can be seen in

¹ For better interpretability of alpha power change scores we investigated EEG alpha activity for each condition separately. There were no treatment-related group differences in brain asymmetry (interactions with Treatment-Group or Time with Hemisphere) for the baseline, neutral, positive, and negative conditions (all $p > .19$). Only for the trauma-related picture there was a significant Treatment-Group x Time x Hemisphere interaction for the anterior region [$F(1,33) = 4.63, p = .04, \eta^2 = .123$]. There were no group differences present for the posterior region.

² Also using the change in BDI-depression score (pre-post) in an analysis of covariance (ANCOVA) the results did not change. Again, for the anterior region there was a tendency for the Treatment-Group x Time x Hemisphere interaction [$F(1,32) = 3.24, p = .08, \eta^2 = .096$]. There was no main effect or interaction with BDI-Change (all $p > .5$).

Figure 3 there was a greater reduction in relative right anterior activation in the CBT patients when compared to Wait-list controls.

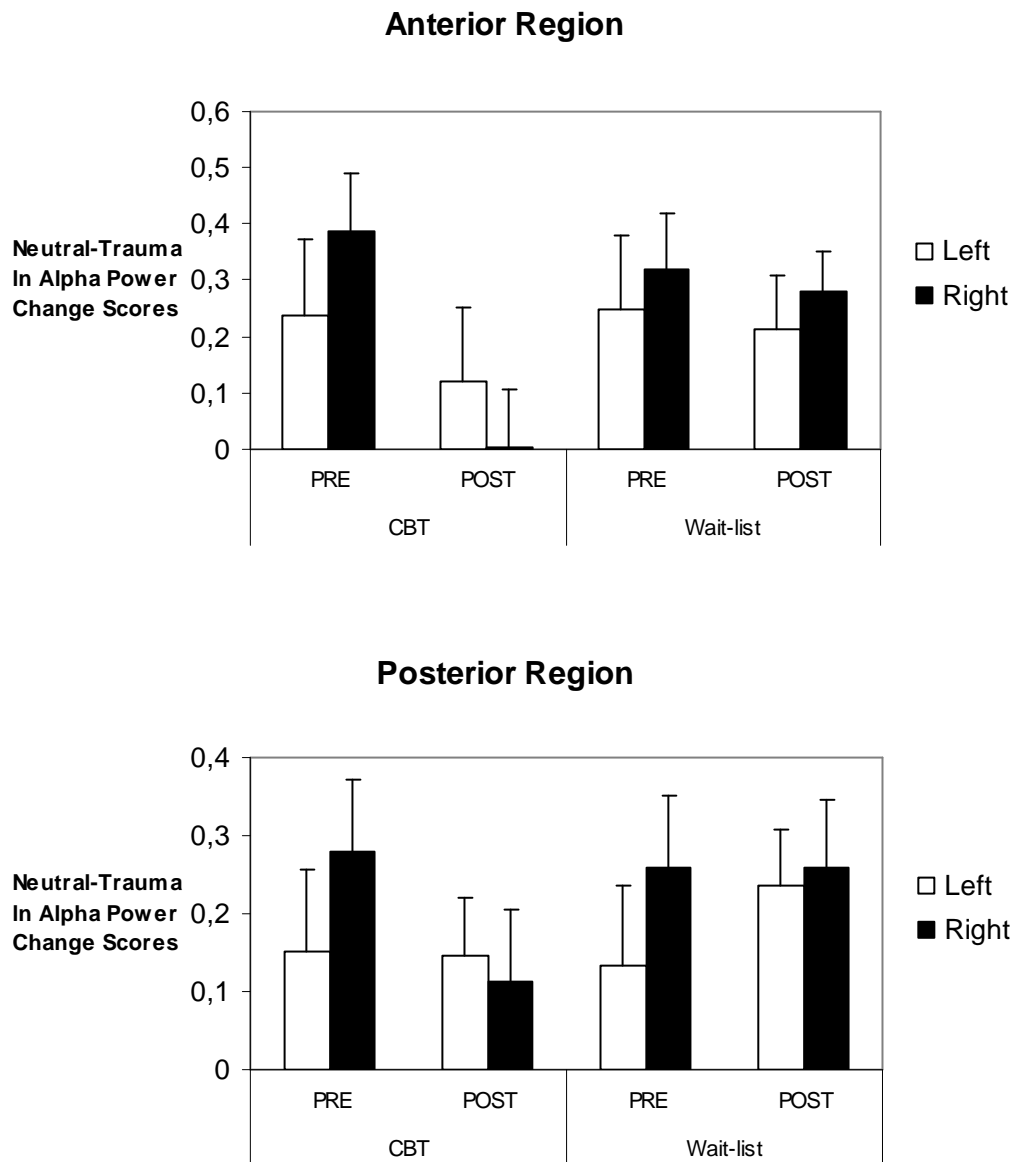


Figure 5. EEG alpha power change scores (neutral minus trauma condition) for the left and right anterior (upper panel) and posterior regions (lower panel) for CBT group and Wait-list controls. Since EEG alpha power is inversely related to activity positive change score values denote increased activation during exposure to the accident picture. Left = left hemisphere; Right = right hemisphere. CBT = Cognitive behavioral therapy; pre = pre-assessment; post = post-assessment. Error bars represent standard errors of the mean.

To test our prediction that the CBT group shows a decrease in hemispheric asymmetry we conducted Time x Hemisphere MANOVAs for each group separately. For the CBT group

there was a significant Time x Hemisphere interaction [$F(1,16) = 7.90, p = .01, \eta^2 = .331$] indicating a shift in hemispheric asymmetry. This interaction was mainly an effect of a decrease in activity in the right [$t(16) = 2.33, p = .03$] but not the left anterior region [$t(16) = 0.69, p = .50$]. The Wait-list showed no change in hemispheric activity over time [Time x Hemisphere interaction: $F(1,17) = 0.01, p = .98$]. For the posterior region there was a tendency for the Time x Hemisphere interaction [$F(1,33) = 3.17, p = .08, \eta^2 = .088$] but no significant Treatment-Group x Time x Hemisphere interaction [$F(1,33) = .13, p = .72$]. Analyses for each group separately revealed no significant Time x Hemisphere interactions for the CBT group [$F(1,16) = 2.78, p = .12$] and Wait-list [$F(1,17) = 0.87, p = .36$] for the posterior region.

The relationship of change in PTSD severity and electrophysiological measures

To examine the relation between changes in EEG measures and PTSD severity we calculated pre-post change scores for measures of a) activation asymmetry, b) activity within the right and left hemisphere, and c) change in PTSD severity (CAPS Score). For these analyses we combined participants from CBT and Wait-list groups ($n = 35$). There was a significant correlation between the decrease in PTSD severity and the total decrease in right anterior activation ($r = .39, p = .02$, see Figure 4). However, there were no significant correlations between change in PTSD severity and total decrease of left hemisphere activation ($r = .26, p = .13$) or change in anterior asymmetry ($r = .08, p = .44$). For the posterior region there was no significant correlation between change in PTSD severity and change in left or right activity and asymmetry (all $r < .18, ps > .31$).

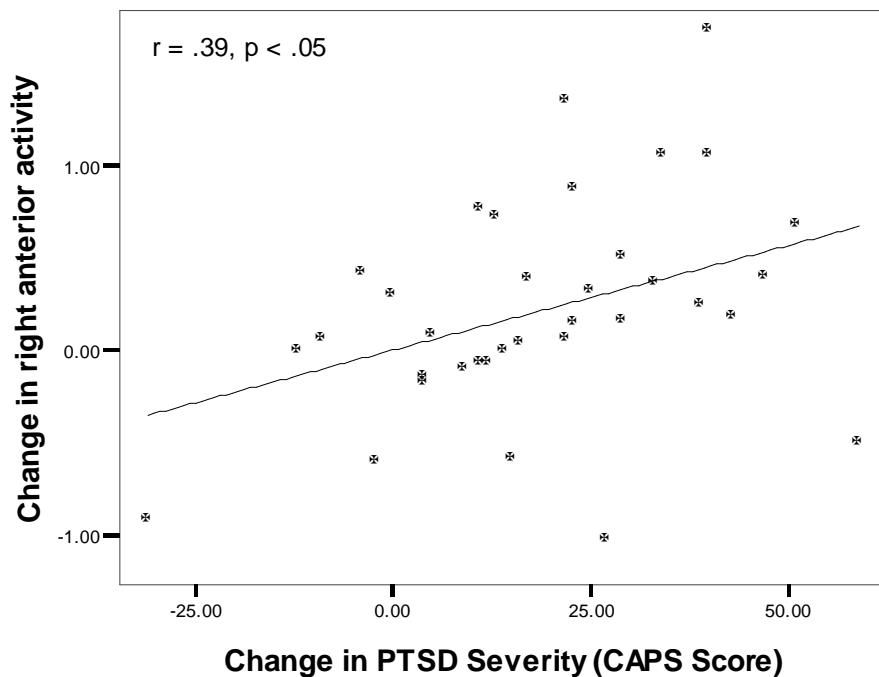


Figure 6. Scatter plot of the association between the reduction in right anterior activation (pre minus post) with the change in PTSD severity (CAPS score). Higher activation change scores indicate greater reduction in activation.

3.2.4 Discussion

This study examined whether increased right-sided hemispheric activation during exposure to a trauma-related accident picture in patients with PTSD and subsyndromal PTSD which was reported previously (Rabe, Beauducel et al., 2006) would change due to a cognitive-behavioral treatment. Therefore, we compared EEG activity before and after CBT (in comparison to an assessment-only Wait-list condition). Our results showed a trend differences in the change of anterior activation asymmetry as a result of treatment. At pre-assessment the CBT group and Wait-list showed a comparable pattern of increased right hemisphere activation. The CBT group showed a shift of hemispheric activity from pre- to post-assessment which was mainly a result of a decrease in right anterior activation. The pattern of hemispheric activation in the CBT group at post-assessment was similar to that observed for MVA victims without PTSD (Rabe, Beauducel et al., 2006). For the Wait-list there was no significant change in hemispheric anterior activation over time. The observed treatment-group differences in changes in anterior brain asymmetry were not modulated by a differential

change in depression. When statistically controlling for change in scores of BDI-depression, the results did not change. Correlational analysis showed that the decrease in PTSD severity was associated with the reduction in total right anterior activation. For posterior cortical regions there was a trend for a reduction in right hemisphere (Time x Hemisphere interaction) activation which was not significantly different between treatment groups. Furthermore, changes in posterior asymmetry or left/right activation were not related to changes in PTSD severity. The reduction of negative affect during viewing the accident picture was significant only for the CBT group, but did not differ significantly from Wait-list controls.

Our results are consistent with a report of functional brain changes due to CBT in patients with spider phobia (Paquette et al., 2003). The authors reported a reduction of activation in the right dorsolateral PFC following CBT, a region which was activated before CBT during exposure to spider videos. They suggested that changes in dorsolateral PFC activation might reflect changes in avoidance and cognitive strategies for the regulation of fear and anxiety evoked by the phobogenic stimulus. Similarly, Prasko et al (2004) reported a decrease of resting glucose metabolism in right hemisphere prefrontal regions in panic patients.

With regard to models of brain asymmetry and emotion (Coan & Allen, 2003b; Davidson, 1998b; Harmon-Jones & Allen, 1998; Heller et al., 2003), the reduction in right prefrontal cortical activation might reflect a decrease in anxiety related withdrawal tendencies in the CBT group. The group-independent reduction in posterior asymmetry might reflect reduced anxious arousal (Heller et al., 1997; Nitschke et al., 1999) in both groups.

The treatment-related alterations of the cortical activation pattern might be associated with changes in the processing of trauma-related information. The right prefrontal cortex is involved in cognitive processes such as episodic memory retrieval, sustained attention, and visual vigilance (for review see, Cabeza & Nyberg, 2000). Accordingly, increased right anterior activation in patients with PTSD and subsyndromal PTSD (before CBT) during exposure to trauma-related stimuli might be a correlate of altered information processing associated with symptoms of intrusion and hypervigilance. In psychological models of PTSD, externally or internally triggered intrusive memories have been described as mostly visual, very vivid and associated with negative emotions (Brewin et al., 1996; Ehlers & Clark, 2000; 1998) in contrast to the structured, verbally accessible nature of “normal” autobiographical memories. Thus, a reduction in right anterior activation as observed in our study could reflect a normalization of these processes due to cognitive-behavioral interventions. The described

changes in brain activation may be the neurobiological underlying of enhanced top-down regulation and reduced bottom up triggering.

CBT has been shown to produce different brain changes than pharmacotherapy in depression (Goldapple et al., 2004). Goldapple et al. argued that CBT seems to affect clinical recovery by top-down mechanisms that modulate the functioning of specific brain regions (e.g. prefrontal cortex and hippocampus). In contrast, pharmacotherapy may target bottom-up processes that are associated with changes in limbic and subcortical brain regions. Future research is clearly warranted comparing psychological therapies for PTSD with pharmacological interventions.

There are a few limitations of our study, however. First, we used a trauma sample of MVA survivors. Replication of our results is needed using other trauma samples. Our samples consisted of a higher percentage of women and the distribution of gender was slightly different between CBT and Wait-list controls. Some patients had comorbid disorders, although a high rate of comorbidity is typical of PTSD (e.g., Kessler et al., 1995) and exclusion would have resulted in a non-representative sample. Future studies using larger samples are clearly warranted to examine the effects of gender and comorbidity on treatment-related changes of brain activity. However, the CBT and Wait-list controls did not differ in the severity of PTSD symptoms, so that effects due to differential statistical regression to the mean can be ruled out.

Second, the use of identical pictures at pre- and post-assessments might have lead to a treatment independent habituation to this stimulus. This might be the reason for a failure to find differences between treatment groups in change of posterior asymmetry and affective ratings of the trauma picture.

Third, the spatial resolution of our scalp recorded electrophysiology is limited and allows rather coarse distinctions of anterior/posterior and left/right cortical activation. Neuroimaging studies of PTSD revealed that PTSD is also associated with dysfunctions in regions not detectable with EEG such as hippocampus and amygdala (for reviews see Hull, 2002; Nutt & Malizia, 2004). Accordingly, there is need for additional research on brain changes due to CBT in PTSD using neuroimaging techniques with higher spatial resolution. However, the EEG has the advantage of being relatively inexpensive and totally non-invasive which makes it ideally suited for studies of repeated measures and larger samples.

In conclusion, this is the first study reporting changes in brain activity in PTSD in a randomized controlled trial of cognitive-behavioral therapy. PTSD severity was significantly

reduced after CBT in comparison to Wait-list controls. Participants receiving CBT displayed a pattern of reduced right anterior cortical activation after treatment, which has been ascribed a crucial role in experience of withdrawal emotions. The amount of reduction in the right anterior region was associated with reduction in PTSD severity. A highly interesting question for future research might be how different components of psychological therapy of PTSD (e.g. cognitive restructuring, imaginal/behavioral exposure, or relaxation training) are related to changes in brain function.

3.3 Study III: Neural correlates of posttraumatic growth after severe motor vehicle accidents*

3.3.1 Introduction

Experiencing or witnessing life-threatening events such as combat, serious accidents, violence or natural disasters may result in posttraumatic stress disorder (PTSD) or other psychopathologic conditions. Research on these negative sequelae of trauma has grown rapidly during the last decades. Furthermore, rapid developments in our understanding of negative emotions and psychopathological conditions have come from the study of neural and other biological correlates of these phenomena.

In contrast, only in recent years, positive changes following trauma and adversity have been studied systematically. They have been reported empirically following highly stressful events like severe physical illness, injury, rape and sexual assault, military combat, natural disasters, and accidents. These positive changes have been labeled posttraumatic growth (PTG) referring to a positive psychological change arising from the struggle with a major life crisis. It refers to changes including an identification of new possibilities, more meaningful interpersonal relationships, increased appreciation of life, changed priorities, an increased sense of personal strength, and growth in the domain of spiritual and existential matters (Tedeschi et al., 1998). These five domains of self-perceived growth can be measured using the Posttraumatic Growth Inventory (PTGI, Tedeschi & Calhoun, 1996). It has been shown that this measure is correlated with other measures of temperament (e.g., trait positive affect, extraversion), coping (e.g., problem-focused coping), and cognitive processing (for reviews, see Linley & Joseph, 2004; Tedeschi & Calhoun, 2004).

Similarly, there is a large body of research focusing neural correlates of negative consequences of trauma like PTSD (e.g., Hull, 2002). In contrast, neural correlates of individual differences in posttraumatic growth are unknown. Models of brain asymmetry and emotion propose that left-hemisphere regions within the prefrontal cortex are part of a circuit involved in approach-related behavior and positive emotion (e.g., Davidson, 1995; Davidson, 2000; Heller et al., 2002). Support for these assumptions comes from studies investigating

* This study is already published (Rabe, Zöllner, Maercker, & Karl, 2006). Reprint of content with permission of the American Psychological Association.

brain asymmetries in the electroencephalogram (EEG). Tonic levels of relative left-sided activation (lower left than right frontal EEG alpha power) have been associated with dispositional positive affect (Tomarken, Davidson, Wheeler, & Doss, 1992), behavioral approach tendencies (Coan & Allen, 2003a; Harmon-Jones & Allen, 1997; Sutton & Davidson, 1997), a self-enhancing coping style (repression) (Tomarken & Davidson, 1994), adaptive emotion regulation (Jackson et al., 2003), enhanced responding to affective stimuli of positive valence (Sutton & Davidson, 2000; Tomarken et al., 1990). For a comprehensive review of neural correlates of well-being and positive affective style see Davidson (2004a).

Recently, Urry et al. (2004) reported an association of greater relative left fronto-central activation and higher levels of psychological (or eudaimonic) well-being (PWB), even when statistically controlling for trait-positive affect. PWB has been introduced recently and described as perception of engagement with existential challenges in life such as pursuing meaningful goals, growing and developing as a person, and establishing quality ties to others (Keyes, Shmotkin, & Ryff, 2002). Urry et al. (2004) suggested that goal-directed approach tendencies (e.g., challenging oneself and striving to achieve in the face of adversity) as reflected by left frontal activation may be important for attaining PWB.

Posttraumatic growth represents an element of psychological well-being (Joseph & Linley, 2005). This positive psychological change in reaction to highly challenging life events is marked by an active change of schemas, beliefs, goals and personal relations. Its subjective acknowledgment requires disengagement from unattainable goals and orientation toward new goals (Tedeschi & Calhoun, 2004). Thus, based on previous findings (Urry et al., 2004), it is conceivable that PTG (as an element of psychological well-being) is associated with relative left frontal brain asymmetry. Summarized, with reference to research highlighting the role of left anterior regions of the cortex in positive emotion, approach-related behavioral tendencies, and psychological well-being we assumed that more relative left-sided frontal activity would be associated with higher levels of posttraumatic growth. Furthermore, we expected that these relations should not just be explained by dispositional positive affect.

3.3.2 Methods

Participants

The participants were 82 survivors of severe motor vehicle accidents (MVA's). Since this report is part of a larger study concerned with psychological and psychophysiological correlates of chronic PTSD we included only persons with the accident dating at least 6

months prior to testing. The average time since the accident was 57 months (SD = 77.1, Range: 6- 474). After a short telephone screening participants were scheduled for a diagnostic session and a psychophysiological recording session. All participants received a comprehensive description of the study and provided written informed consent at the initial diagnostic assessment. The protocol was approved by the ethics board of the Dresden University of Technology.

Exclusion criteria for the study were a history of neurological disorders or brain damage during the accident, current alcohol and/or substance abuse or dependence, current or past schizophrenic, bipolar, or psychotic disorder. All participants were required to be off all psychotropic medication for at least 1 month before testing. All participants were right-handed as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). In the current analyses we included participants meeting the diagnostic criteria for full PTSD (n = 23; 19 females) or subsyndromal PTSD (n = 22; 16 females). For classification details see (e.g., Blanchard, Hickling, Taylor, Loos, & Gerardi, 1994)³. Thirty-seven participants (20 females) received no PTSD diagnosis⁴.

Measures

Diagnostic Interviews. During the diagnostic session, first an accident-interview was conducted asking for details of the accident and injuries. PTSD status and severity were assessed by a German version (Schnyder & Moergeli, 2002) of the Clinician Administered PTSD Scale (CAPS) (Blake et al., 1995). The Structured Clinical Interview for the DSM-IV

³ Nine participants with PTSD met criteria for current major depression (MDD) and 4 met criteria for lifetime MDD. Additional diagnoses within the PTSD group were dysthymia (n = 2), panic disorder without agoraphobia (n = 2); panic disorder with agoraphobia (n = 1), agoraphobia without panic disorder (n = 2), social phobia (n = 2), specific phobia (n = 5), lifetime generalized anxiety disorder (n = 1), and obsessive compulsive disorder (n = 1). Additional diagnoses in the subsyndromal PTSD group were MDD (n = 4), agoraphobia without panic disorder (n = 1), social phobia (n = 2), and specific phobia (n = 2). Two of the non-PTSD participants met the criteria for mild current specific phobia and 1 for mild social phobia (n = 1). Lifetime but not current diagnoses within the non-PTSD group were PTSD (n = 16), MDD (n = 12), panic disorder without agoraphobia (n = 1), social phobia (n = 2), and generalized anxiety disorder (n = 1). The high rate of comorbidity observed in PTSD participants is typical of this disorder (e.g., Kessler et al., 1995).

⁴ Twenty-two PTSD subjects, 21 subsyndromal PTSD subjects, and 23 of the non-PTSD subjects included in the analyses for the present paper were also included in previously reported analyses concerning PTSD-group differences in brain asymmetry (Rabe, Beauducel, Zöllner, Maercker, & Karl, 2005).

(SCID) (First et al., 1996; Wittchen et al., 1997) evaluated the presence of concurrent and lifetime DSM-IV Axis I disorders.

Self-Report Measures. Several self-report questionnaires were sent to the participants prior to the diagnostic interview session including measures of personality and of symptoms of PTSD, anxiety, depression. Only those relevant for the current report are described as followed.

The German version (Maercker & Langner, 2001) of the Posttraumatic Growth Inventory (PTGI) (Tedeschi & Calhoun, 1996), is a 21-item scale to assess the degree of reported positive changes experienced in the struggle with the traumatic event. It measures growth across five domains: New Possibilities ($\alpha = .81$), Changed Relationships ($\alpha = .87$), Appreciation of Life ($\alpha = .59$), Personal Strength ($\alpha = .81$), and Spiritual Changes ($\alpha = .85$). Participants rated their experience of growth on a 5-point response format ranging from 0 = not at all to 4 = much. For the total scale coefficient alpha was .92 in this sample.

Trait and state affect were assessed by an extended (24-items) German version (Krohne et al., 1996) of the Positive and Negative Affect Schedule (PANAS) (Watson et al., 1988). Trait positive affect (T-PA; $\alpha = .91$) and trait negative affect (T-NA; $\alpha = .90$) were assessed using 12 adjectives for each scale. To assess trait affect participants were asked to describe how they generally experience feelings (ranging from 1 = very slightly to 5 = extremely). State affect was assessed by asking participants how they felt during the baseline measurement.

Procedure

EEG baseline data were obtained prior to the start of an emotion induction and an event-related-potential experiment including exposure to trauma-related pictures. EEG was recorded in an electrically shielded room with dimly light while participants were resting in a comfortable arm chair. The baseline recording procedure was kept similar to Tomarken, Davidson, Wheeler, and Kinney (1992). Participants were informed that there would be eight 1 min resting baselines, four with eyes open four with eyes closed and where asked to minimize eye blinks and movements. No other specific instructions concerning the baselines were given. Two randomly assigned, counterbalanced orders were used for eyes open (O) and eyes closed (C) trials of the resting baselines (C-O-O-C-O-C-C-O, O-C-C-O-C-O-O-C). Participants heard a tone denoting the beginning and a double tone denoting the end of each 1-min recording. During the 20 s lasting breaks between the baselines, participants were informed via PC monitor whether the following period was eyes open or eyes closed.

Immediately after the final resting period, baseline mood was assessed with the PANAS-state questionnaire.

Electrophysiological Recording and Analysis

EEG was recorded from 28 scalp placements (Fp1, Fp2, F7, F3, Fz, F4, F8, Fc5, Fc1, Fc2, Fc6, T7, C3, Cz, C4, T8, Cp5, Cp1, Cp2, Cp6, P7, P3, Pz, P4, P8, POz, O1, O2) according to the extended 10-20 system (Pivik et al., 1993) using a stretchable electro cap (FMS, Falk Minow Services, Munich, Germany). Moreover, we recorded EEG activity at linked mastoid positions (A1, A2). All sites were referenced to a computer averaged F3/F4 reference and grounded at AFz. Impedances were maintained below 5 k Ω and within 500 Ω at homologous sites. The EEG signal was recorded by a Nihon Kohden amplifier (NeuroFileII system), filtered with a time constant of 10 s and a high frequency cut-off (300 Hz), digitized online at 1024 Hz, and stored at 256 Hz.

A linked-mastoids reference was rederived offline. Before further data processing, EEG artifacts (eye blinks and muscle artifacts) were removed by applying the independent component analysis (ICA) (Jung et al., 2000) to the EEG segments of interest. Prior to artifact screening, an offline bandpass filter (1 to 30 Hz) was applied. Continuous EEG data were divided offline in 4 s epochs (50 % overlap) and again visually inspected for artifacts. All epochs free of artifacts were subjected to a fast Fourier transformation (FFT) using a Hamming window over the distal 50% of each epoch. By averaging segments, estimates of spectral power (μV^2) were derived for 0.25 Hz bins, averaged between 8-13 Hz, and normalized (natural log) to obtain ln power density ($\ln \mu\text{V}^2/\text{Hz}$) in the alpha band (Gasser et al., 1982). Asymmetry indices (\ln right - \ln left) were calculated for each homologous electrode pair separately. Alpha power is considered to be inversely related to cortical activity, with decreases in alpha power reflecting increases in activation (Davidson, Chapman, Chapman, & Henriques, 1990). Therefore, higher scores of the asymmetry index indicate relatively higher left cortical activity.

Table 8: Correlation between Alpha Asymmetry at the Fronto-central Region and Age, PTSD-Severity, Measures of Posttraumatic Growth, Trait- and State Affect

	Mean	SD	Range	Asymmetry (Fc2 - Fc1)	p
Age	41.54	13.19	19 - 72	.01	.90
PTSD - Severity (CAPS)	28.26	21.75	0 - 81	-.06	.61
PTGI - SUM	37.88	16.88	6 - 78	.34	< .001 ^b
New Possibilities	7.32	4.80	0 - 20	.41	< .001 ^b
Changed Relationships	14.23	7.15	0 - 28	.31	< .01 ^b
Appreciation of Life	7.57	2.61	1 - 12	.23	< .05 ^b
Personal Strength	6.52	3.91	0 - 15	.30	< .01 ^b
Spiritual Changes	2.24	2.58	0-8	-.07	.26 ^b
Trait - Positive Affect ^a (T-PA)	40.91	7.72	17 - 57	.20	.08
Trait - Negative Affect (T-NA)	27.23	8.77	12 - 49	-.16	.15
Baseline - Positive Affect	33.28	7.52	18 - 51	.02	.84
Baseline - Negative Affect	14.59	3.40	12 - 26	-.09	.44

CAPS = Clinician Administered PTSD Scale; PTGI = Posttraumatic Growth Inventory; ^a n = 80; ^b one-tailed Pearson product-moment correlations, All other correlations are two-tailed.

3.3.3 Results

Correlation of Fronto-central asymmetry with posttraumatic growth, and other measures

Based on previously reported associations between psychological well-being and fronto-central asymmetry (Urry et al., 2004) we restricted our statistical analysis to the fronto-central asymmetry score (Fc2 - Fc1). We predicted that greater PTG scores should be associated with greater relative left fronto-central activity (positive correlations). For examination of our hypotheses one-tailed Pearson product-moment correlations were computed. For all other exploratory analysis, we used two-tailed correlations. Table 8 shows correlations between fronto-central EEG alpha asymmetry and age, PTSD-severity and measures of posttraumatic growth, trait affect, and baseline affect.

As predicted, there were significant positive correlations between fronto-central alpha asymmetry and posttraumatic growth (PTGI-SUM) indicating that greater relative left cortical activity was associated with more PTG. As can be seen in Table 8 and Figure 5, significant positive correlations were revealed between fronto-central asymmetry and four of the five PTGI dimensions (New Possibilities, Changed Relationships, Appreciation of Life, Personal Strength). Additionally, a tendency for a positive correlation was observed between fronto-central asymmetry and T-PA.

The role of comorbidity and gender

When excluding participants with any current DSM-IV Axis I comorbidity except PTSD (resulting sample $n = 54$) the associations between PTGI and fronto-central asymmetry were essentially the same as for the total sample with 5 of 6 (again not spiritual changes) significant correlations. In order to address the question whether reversible neurological trauma in our MVA sample could have affected our results we excluded subjects with concussion ($n = 19$) or loss of consciousness ($n = 33$). The findings for the resulting sample ($n = 45$) were essentially the same as for the total sample with significant associations (or tendencies) between PTGI and fronto-central asymmetry for 5 of 6 PTGI scales (again not spiritual changes).

The majority of the participants was female ($n = 52$). Accordingly, it was of interest to know if the effects were similar between two sexes. Therefore, we computed correlations between PTGI and fronto-central asymmetry within men and women. In the two groups the pattern of results was similar to that for the total sample. Two-tailed comparisons (Fisher's z) for differences between correlations yielded no significant differences in correlations between men and women (all $p > .26$). Furthermore, it was interesting whether the pattern of correlations was influenced by PTSD diagnosis. Therefore, we computed correlations within subjects with PTSD or subsyndromal PTSD ($n = 45$) and without PTSD diagnosis ($n = 37$). Again, two-tailed comparisons (Fisher's z) for differences between correlations yielded no significant differences in correlations between these two groups.

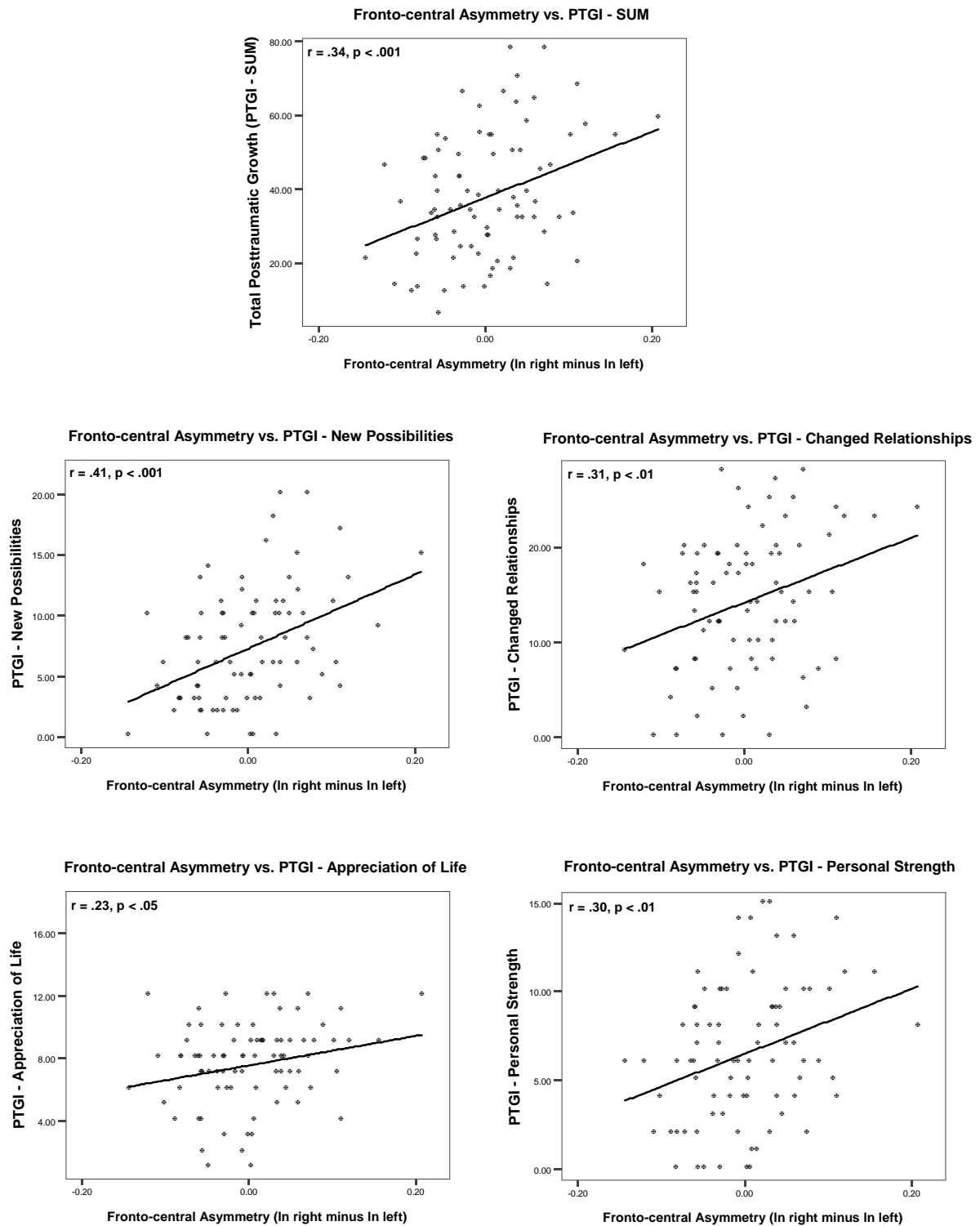


Figure 7. Scatter plots of fronto-central (Fc2-Fc1) asymmetry scores with total Posttraumatic Growth (PTGI-SUM) and the PTGI dimensions: New Possibilities, Changed Relationships, Appreciation of Life, and Personal Strength. More positive asymmetry scores indicate greater relative left-sided activity.

Correlation between PTGI-scales and other measures

Total posttraumatic growth (PTGI-SUM) was not related to age, T-NA, and baseline affect (all $p > .54$). There was a statistical trend for the association of total posttraumatic growth with T-PA ($r = .19$, $p = .09$). T-PA was also positively associated with the PTGI dimensions New Possibilities ($r = .25$, $p < .05$) and Personal Strength ($r = .32$, $p < .01$) but not others (all $p > .34$). Furthermore, there was a negative correlation between PTGI - Personal Strength and PTSD-Severity ($r = -.23$, $p = .04$). No association between PTGI-Scales and other measures reached significance (all $p > .12$).

Partial correlations between EEG asymmetry and posttraumatic growth (with T-PA partialled out)

We were interested whether the relationship of posttraumatic growth and fronto-central EEG asymmetry was independent of T-PA. Accordingly, we computed first order partial correlations using T-PA as covariate. As predicted, there were positive correlations between fronto-central asymmetry and PTGI-SUM score ($r = .29$, $p < .01$), and four PTGI dimensions: New Possibilities ($r = .37$, $p < .01$), Changed Relationships ($r = .26$, $p < .05$) Appreciation of Life ($r = .24$, $p < .05$), Personal Strength ($r = .25$, $p < .05$) but not Spiritual Changes ($p = .20$).

Exploratory analyses of other brain regions

To explore relationships between brain asymmetry of other brain regions and posttraumatic growth we computed two-tailed product-moment correlations. There were significant positive associations between PTGI-SUM-score and asymmetry scores in the fronto-central-lateral (Fc6-Fc5; $r = .24$, $p < .05$), and central region (C4-C3; $r = .25$, $p < .05$) and a statistical trend for anterior temporal asymmetry (T8-T7; $r = .19$, $p = .09$).

3.3.4 Discussion

The results of this study confirmed our initial hypothesis that greater relative left baseline prefrontal activation, as indexed by EEG alpha power asymmetry, corresponds with greater self-perceived posttraumatic growth as reflected in the PTGI scale. In addition, our data shows that the different domains of posttraumatic growth are differentially related to anterior asymmetry. Relative left fronto-central activity was associated with New Possibilities, Changed Relationships, Appreciation of Life, and Personal Strength but not Spiritual Changes.

Dispositional positive affect was also associated with greater relative left-sided fronto-central activity. This is consistent with reports of relations of greater left than right frontal activation with dispositional positive affect (Tomarken, Davidson, Wheeler, & Kinney, 1992; Urry et al., 2004). However, previous studies demonstrated that there are stronger associations between relative left-frontal activity and those constructs not captured by dispositional positive affect such as behavioral approach (Coan & Allen, 2003a; Harmon-Jones & Allen, 1997; Sutton & Davidson, 1997) or repressive coping style (Tomarken & Davidson, 1994). Likewise, psychological well-being, which has been linked to posttraumatic growth (Joseph & Linley, 2005), has been shown to be predicted by fronto-central alpha asymmetry, even after controlling for T-PA (Urry et al., 2004). These results were interpreted as evidence that goal-related approach tendencies, reflected in frontal brain asymmetry, may be important for attaining psychological well-being. Similarly, we found a positive association between relative left fronto-central activity and posttraumatic growth which was not altered substantially when positive affect was statistically controlled. Furthermore, there was only a weak association between T-PA and posttraumatic growth. Taken together, our results suggest that posttraumatic growth as measured by the PTGI does not represent just dispositional positive affect but might be better explained by approach-related tendencies reflected by relative left frontal activity. Sutton and Davidson (1997) have argued that persons with tonically more active left prefrontal regions may be more likely to organize limited resources in support of goal-approaching behaviors and thoughts. This may promote the subjective acknowledgement of positive changes experienced in the aftermath of traumatic events like a severe MVA. In accordance with Davidson (1995), who proposed that relative left frontal activity reflects goal-directed approach tendencies, our results support the assumption that PTG might reflect a process of active struggling toward new goals and perspectives for the self. Accordingly, especially the more goal-directed dimensions of PTG (e.g., the PTGI subscale New Possibilities) might be associated with anterior frontal brain asymmetry. In contrast, the PTGI subscale Spiritual Changes, which was not associated with anterior brain asymmetry, might be unrelated to approach tendencies and rather reflect a higher order cognitive construct of PTG of giving up control or handing it over to a higher power.

However, research is needed to explore the possible mechanisms underpinning the association of frontal brain asymmetry with PTG. For this, two potential directions are conceivable: First, a collateral assessment of PTG and individual differences variables that have been linked to anterior asymmetry (behavioral approach, emotional responding,

repressive coping, measures psychological well-being). Second, individual differences in anterior brain asymmetry may play an important role in emotion- and stress-regulation. Greater relative left anterior activity has been associated with biological indices of reactivity to stressful events such as (a) better recovery following an aversive event (emotion-induced eye-blink startle) (Jackson et al., 2003); (b) lower levels of baseline cortisol (Kalin et al., 1998); (c) greater antibody responses to influenza vaccine (Rosenkranz et al., 2003); greater levels of natural killer cell activity and smaller decline of natural killer cell activity in response to stress (Davidson et al., 1999). There is furthermore evidence that left prefrontal activation is essential for the use of cognitive reappraisal to decrease affective responses to highly negative scenes (Ochsner, Bunge, Gross, & Gabrieli, 2002). Given the relation between anterior brain asymmetry and PTG found in our study we suggest that a focus for further research might be how stress-related and health-related biological indices are linked to PTG. To our knowledge there is only one study of this kind in which Epel, McEwen, and Ickovics (1998) could show that PTG was related to an adaptive cortisol response to stress.

Some limitations of the study should be noted. First, we used a sample of MVA-survivors at least 6 month post-accident. Therefore, the generalizability of our results remains to be demonstrated with respect to (a) trauma samples other than MVA-survivors and to (b) different stages of posttraumatic adaptation.

Second, our study was clearly cross-sectional and does not permit causal inferences about the relationship between brain asymmetry and posttraumatic growth. Baseline alpha asymmetry has been conceptualized as trait marker of affective style with excellent internal consistency reliability and acceptable test-retest stability (Tomarken, Davidson, Wheeler, & Kinney, 1992). However, there is evidence for plasticity in the circuits involved in emotion regulation (for review see Davidson, 2000). Thus, it remains unclear if trait-like brain asymmetry promotes posttraumatic growth or growth-related changes alter patterns of brain activity. A focus for additional research should be the longitudinal investigation of the association between brain mechanisms and posttraumatic growth.

Third, though the EEG has some advantages one of its limitations is the poor spatial resolution. EEG is completely noninvasive, relatively inexpensive and may provide information about hemispheric differences of relatively broad regions of the cortex. This makes it ideally suitable for studies with large samples and longitudinal research. Using hypotheses-guided and exploratory EEG analyses we were able to reveal that greater PTG was associated with relative left fronto-central activation and relative left-sided activity of

additional anterior regions (fronto-central lateral, central, and a statistical trend for the anterior temporal region), but not posterior regions. For some of these regions associations with measures of affective-style have been revealed (for review see Coan & Allen, 2003b). However, for a more definitive understanding of the cortical sources of scalp-recorded electrophysiology, high density EEG recordings in combination with source localization techniques are warranted. Moreover, the EEG is limited for recording activity of regions that have been suggested to be involved in emotion regulation and PTSD pathophysiology such as the amygdala, hippocampus, and medial prefrontal cortex. Studies using neuroimaging techniques with better spatial resolution are needed for a more definitive understanding of the brain structures involved in PTG.

To our knowledge this is the first study relating measures of brain function to posttraumatic growth. We have demonstrated that relative left frontal cortical activation is associated with higher values of PTG in a large sample of MVA survivors. These relations were also present after controlling for T-PA. We assume that the left hemispheric self regulatory system, which mediates approach and positive affect, facilitates the achievement of growth. Furthermore, the results indicate that EEG alpha asymmetry may be useful in discriminating different dimensions of posttraumatic growth. We suggest that future research using neuroscience methods might help to clarify the mechanisms that support posttraumatic growth.

4 Summary, General Discussion*

In this thesis three studies have been presented investigating the association of EEG alpha asymmetry with: (1) PTSD and its symptoms; (2) change in PTSD severity due to CBT; (3) Posttraumatic Growth in MVA survivors. Furthermore, the results have been discussed critically with respect to observed findings from recent literature and models of brain asymmetry and emotion. The discussion of the results included a consideration of limitations of the studies with regard to: sample, stimulus material, limits of EEG recordings and will not be repeated here. The following chapter will shortly summarize the results of the 3 studies. Furthermore, some generally important issues in this area of research will be considered such as (1) the relation of the results to the state-trait debate of EEG asymmetry; (2) the connection of the results to psychological theories of PTSD and PTG; and (3) the use of brain research for psychotherapy. Suggestions for further research will be discussed in these sections.

4.1 Summary of the empirical results

Study I examined EEG alpha asymmetry among MVA survivors with PTSD, with subsyndromal PTSD, and without PTSD as well as non-exposed healthy controls during baseline and in response to neutral, positive, negative, and trauma-related pictures. Based on research highlighting the role of right anterior regions in withdrawal-related emotions (Davidson, 1998b) and right posterior regions in anxious arousal (Heller et al., 2003), we expected that patients with PTSD and subsyndromal PTSD would exhibit increased activation (i.e. EEG alpha reduction) of right hemisphere anterior and posterior regions during exposure to a trauma-related picture. On the basis of previous findings highlighting the role of resting brain activity as a trait marker for psychopathology (for review see Coan & Allen, 2003b), we assumed that PTSD and subsyndromal PTSD patients would show increased relative right anterior and posterior baseline activity. In accordance with our first hypothesis, both PTSD and subsyndromal PTSD patients displayed a pattern of increased right-sided anterior activation during the trauma-related condition which was similar to that previously reported in patients with PTSD (McCaffrey et al., 1993) and other anxiety disorders (Davidson, Marshall

* Parts of this chapter are already submitted for publication (Rabe & Karl, submitted)

et al., 2000; Wiedemann et al., 1999) during symptom provocation. Our finding of increased relative right posterior activation in PTSD and subsyndromal PTSD was consistent with recent studies reporting right posterior activation during anxiety-provoking situations in anxious participants (Davidson, Marshall et al., 2000; Heller et al., 1997). Furthermore, posterior asymmetry in non-traumatized healthy controls varied with gender, with female participants showing a pattern of higher right posterior activation. Although not expected, the finding underscores the importance of this variable in EEG asymmetry research (Davidson et al., 1976; Miller et al., 2002). Contrary to our second hypothesis, we observed no group differences in EEG alpha activity during rest which was assumed because of recent findings in a PTSD sample (Metzger et al., 2004) and other anxiety populations (Wiedemann et al. 1999). However, this finding is in accordance with a recent study that also failed to show abnormalities in baseline asymmetry in PTSD subjects (Shankman et al., 2008).

In the second study it was examined whether increased right-sided hemispheric activation during exposure to a trauma-related accident picture in patients with PTSD and subsyndromal PTSD which was reported in study I would change due to CBT. Therefore, we measured EEG activity before and after CBT (in comparison to an assessment-only Wait-list condition) as part of a previously completed controlled, randomized treatment trial for MVA-related PTSD (Maercker et al., 2006). As predicted, there was a change in relative right anterior activation in the CBT group but not the Wait-list group. However, both groups showed a reduction in relative right posterior activity. Across both groups, reduction of PTSD symptoms due to therapy was correlated with a decrease in right anterior activation during trauma-related stimulation. The pattern of relative reduced right hemisphere activation after therapy in the CBT group was similar to that observed in MVA victims without PTSD in study I. Several explanations for this change in brain activation were outlined in the discussion section (chapter 3.2.4) ranging from simple reduction of avoidance tendencies to adaptive information processing.

In the third study, an exploratory analysis was presented on the relation of anterior resting asymmetry and subjective perception of Posttraumatic Growth after MVAs. Based on research highlighting the role of left anterior regions of the cortex in positive emotion, approach-related behavioral tendencies and personal well-being (Coan & Allen, 2003b; Urry et al., 2004), we expected that higher relative left-sided anterior activity would be associated with higher levels of PTG. The results confirmed our prediction. It was reported that relative left frontal cortical activation was related to the sum score of the PTGI scale, a measure of

PTG. In addition, our data showed that the different domains of PTG were differentially related to anterior asymmetry. Although, there was also a relation between anterior asymmetry and trait positive affect, the relations with PTG were also present after controlling for positive affect. In the discussion, it was suggested that trait-like resting relative left prefrontal activity, which has been associated with goal-directed approach tendencies (Sutton & Davidson, 1997), may promote adaptive emotion-regulation (Jackson et al., 2003; Ochsner, Bunge, Gross, & Gabrieli, 2002) and thus facilitate the achievement of growth after traumatic events.

In conclusion, study I showed a context-dependent (trauma-specific) alteration of hemispheric activation in symptomatic MVA-survivors (patients with PTSD and subsyndromal PTSD) which was associated with anxious arousal and symptoms of PTSD. The new feature of this study was the parallel assessment of trait (resting baseline) and state (emotion induction) measures of EEG asymmetry in a relatively large sample of MVA survivors. Furthermore, this was also the first study assessing brain asymmetry in PTSD which used two control groups (healthy controls with and without MVAs) and results were compared between subsyndromal PTSD and full PTSD. To the author's knowledge, study II presents the first study reporting changes in brain activation (assessed by EEG alpha activation) in subjects with PTSD and subsyndromal PTSD in a randomized controlled trial of cognitive-behavioral therapy. The CBT group showed a pattern of reduced right anterior cortical activation after treatment and the amount of reduction in the right anterior region was associated with reduction in PTSD severity. Study III was the first study relating measures of brain function to self perceived Posttraumatic Growth. It was shown that relative left-sided resting anterior activity is related to higher values of PTG in MVA survivors. In summary, the three studies suggest that measures of EEG asymmetry may be useful for the understanding of brain mechanisms that may underlie positive and negative consequences of psychological trauma as well as changes due to successful psychological treatment.

4.2 The relation of trait and state asymmetry with PTSD and PTG

In study I, we predicted that PTSD and subsyndromal PTSD would differ from healthy controls in trait (baseline) EEG asymmetry and EEG asymmetry as state measure during exposure to a trauma relevant stimulus. However, we only found group differences in EEG alpha asymmetry during an emotional state but not during baseline. Furthermore, as shown in

study II changes in PTSD severity due to CBT were associated only with changes in state-related but not trait-like baseline EEG asymmetry.

It has been hypothesized that resting EEG asymmetry represents a trait-like vulnerability factor or diathesis that is associated with risk for emotion-related psychopathology (e.g. Davidson, 1998a). This proposal has been extensively tested for depression showing that relative reduced left frontal activity characterizes depressed individuals not only when depressed, but also when in remission or when successfully treated (Allen et al., 2004; Bruder, 2003; Coan & Allen, 2003b; Davidson, Pizzagalli, Nitschke, & Putnam, 2002). However, our findings suggest that baseline EEG may not represent a trait marker which is associated with risk for PTSD. Thus, measures of baseline EEG asymmetry may differentiate between psychopathologic conditions as PTSD and depression, although PTSD is associated with a high comorbidity of depression. This is in line with research showing that these two conditions may exhibit different biological correlates such as HPA function (e.g. Yehuda, 2006). Furthermore, resting EEG asymmetry may be a distinguishing biological marker for certain anxiety disorders. For example, there have also been no differences in baseline asymmetry in social phobics (Davidson, Marshall et al., 2000) but in patients with panic disorder (Wiedemann et al., 1999), individuals high in trait anxiety (Blackhart et al., 2006), or with high trait levels of anxious arousal (Nitschke et al., 1999). Our results of no association of PTSD with trait asymmetry have been replicated recently in a study also reporting no PTSD-associated trait-like brain asymmetry in a mixed sample of patients with civilian trauma (Shankman et al., 2008). However, it is in contrast with previous research showing that posterior baseline asymmetry would be associated with PTSD hyperarousal in Vietnam war nurse veterans (Metzger et al., 2004). Reasons for discrepant findings may be variables like: type of trauma (civilian vs. combat), chronicity of PTSD, and time since trauma. This is of interest because research using other psychophysiologic measures (e.g. heart rate) showed that tonic psychophysiologic activity in PTSD may be dependent on variables such as types of trauma and chronicity of the disorder (Buckley & Kaloupek, 2001; Orr et al., 2002; Pole, 2007). In contrast, psychophysiologic reactivity to trauma-related stimuli is a well replicated finding in PTSD (Pole, 2007) and especially in MVA-related PTSD (Blanchard, Hickling, Buckley et al., 1996; Rabe, Dorfel, Zollner, Maercker, & Karl, 2006; Veazey, Blanchard, Hickling, & Buckley, 2004). Thus, baseline EEG asymmetry may discriminate between different PTSD samples, which could be a field for further investigation.

A further possibility of our non-significant baseline finding could be that the sample size was too small to detect an existing effect. However, our analyses had 79% power to detect a medium effect size (Thibodeau et al., 2006) for PTSD severity ($n = 64$), and 88% power to detect a medium effect size for depression (BDI, $n = 85$). This suggests that our non-significant baseline findings are rather not due to a type II error (the probability of falsely accepting H_0 when in fact H_1 is true).

Summarized our findings suggest, that individuals with MVA-related PTSD or subsyndromal PTSD do not exhibit abnormal affective traits (as general withdrawal tendencies or general hyperarousal), but show abnormal trauma-specific affective states, which changes due to CBT.

In contrast to PTSD, there was a relation of trait-like resting anterior asymmetry and dimensions of posttraumatic growth. Thus, instead being a risk factor for the development of PTSD, resting brain asymmetry might rather promote the development of PTG. As discussed in chapter 3.3.4, especially the approach- or goal-oriented dimensions of PTG (e.g., the PTGI subscale New Possibilities) seemed to be associated with anterior trait asymmetry, which is consistent with the model of Davidson (1998b; 2000), proposing that trait-like left anterior activation represents a disposition to experience rather positive and especially with approach-related emotions. However, the assumption that baseline brain asymmetry represents such a predisposition can only be answered using longitudinal designs. For example, studies are suggested that may assess brain asymmetry in persons with high risk for traumatic experiences (e.g. fire fighters) and examine later growth in response to stress. In another design one might assess brain asymmetry shortly after traumatic experience and assess later development of PTG. Finally, it must be noted, that there is certainly no one single brain characteristic that predicts development of PTG. Rather, recent evidence suggests that posttraumatic growth is a dynamic process across time (Helgeson et al., 2006). Thus, it is suggested that the development of growth involves several psychological and biological processes that may interact and also may vary across time.

4.3 The relation brain asymmetry findings to psychological models of PTSD and PTG

As reviewed in chapter 2.5 and 2.6, recent theories of PTSD based on neuroimaging findings are often etiologically reductionistic, suggesting PTSD might be just a manifestation of

altered function of some brain regions (see chapter 2.6.1). Furthermore, there is only little convergence of psychological and neurobiological research of PTSD (for exception see Brewin, 2001, 2008). Thus, the current chapter tries to connect the findings of the empirical studies (I, II, III) with psychological theories of PTSD and PTG.

With regard to models of brain asymmetry and emotion (Coan & Allen, 2004; Davidson, 1998b; Heller et al., 2003) study I showed that trauma-specific right anterior activation in PTSD and subsyndromal PTSD might reflect the activation of a brain system involved in avoidance–withdrawal tendencies and right posterior activation may reflect activation of a system mediating anxious arousal. Study II suggests that the treatment-related reduction in right frontal cortical activation might reflect a decrease in anxiety-related withdrawal tendencies in the CBT group. However, what might be a link of EEG asymmetry research and models of PTSD? First, as reviewed in chapter 2.5 nearly all recent psychological models propose that avoidance of trauma-related stimuli, situations, and thoughts is a key factor for development and maintenance of PTSD (Brewin & Holmes, 2003; Ehlers & Clark, 2000; Foa & Rothbaum, 1998). Thus, right anterior activation in PTSD and subsyndromal PTSD subjects may be the neural correlate of anxiety-related avoidance. Furthermore, the reduction of right anterior activation in the CBT group (study II) might reflect decreased anxiety and a disruption of avoidance tendencies in response to trauma-relevant stimuli due to successful treatment. A second link to psychological models might be the association of brain asymmetry and information processing. Whereas the left hemisphere might be specialized for processing of verbal information, the right hemisphere seems to be specialized for processing of visuo-spatial information. Furthermore, especially the right prefrontal cortex might be involved in cognitive processes such as episodic memory retrieval, sustained attention, and visual vigilance (Cabeza & Nyberg, 2000; Hugdahl & Davidson, 2003). Psychological models of PTSD propose that altered information processing and memory might play a central role in understanding key features of PTSD as reexperience symptoms (see chapter 2.5). These models propose that externally or internally triggered are mostly visual, very vivid, and associated with negative emotions (Brewin & Holmes, 2003; Ehlers & Clark, 2000). In contrast, ordinary autobiographical memories are structured and the sensory elements are verbally accessible and integrated into a personal narrative. Additionally they seem to be at least in part dependent on functioning of the left hemisphere (Maguire, 2001; Piefke & Fink, 2005). Thus, enhanced right anterior activation during processing of trauma-related information in PTSD subjects could be a correlate of nonverbal-emotional

information processing and memory observed in PTSD. Furthermore, reduction in right anterior activation in the CBT group of study II could reflect a normalization of these processes due to therapy.

To further test these assumptions a joint assessment of brain activity and psychological processes based on models of PTSD might be useful. Future studies should evaluate brain activity during manipulation of avoidance strategies that are postulated to maintain PTSD such as thought-suppression, safety seeking behaviors, or distraction. Although there are some studies examining brain function (e.g. hippocampal) during tasks that are thought to activate certain brain structures (e.g. Astur et al., 2006; Bremner, Vythilingam, Vermetten, Southwick, McGlashan, Staib et al., 2003; Geuze, Vermetten, Ruf, de Kloet, & Westenberg, 2008; Shin, Shin et al., 2004), studies are lacking directly linking psychological models of PTSD with measures of brain function. Current neurobiological models (see chapter 2.6.1) tend to focus on symptoms, since most of the neuroimaging studies used symptom provocation paradigms. Thus, studies are needed directly examining brain function during cognitive processes (cognitive activation paradigms) which have been proposed by psychological models to be central for development of PTSD such as data-driven vs. conceptually-driven processing of traumatic information (Ehlers & Clark, 2000) or verbal vs. visuo-spatial encoding (Holmes et al., 2004).

Conceptually, the potential connection between research of PTG and EEG asymmetry is intuitively appealing. There are several theoretical links between PTG and anterior brain asymmetry research. Both, PTG and anterior asymmetry have been associated with concepts as well-being and positive affect. Within the theoretically framework of well-being, PTG has been postulated to represent an element of psychological well-being (Joseph & Linley, 2005). In this view growth and distress may be two independent dimensions of well-being and thus, PTG may co-occur with distress. In fact, findings of a recent meta-analysis showed that perceived growth was unrelated to anxiety and indexes of distress, but positive related to positive affect and less depression but more PTSD symptoms (intrusions and avoidance) (Helgeson et al., 2006). The results of study III support the link of PTG with psychological well-being and positive affect. The latter two concepts also have been found to be associated with anterior asymmetry (Tomarken, Davidson, Wheeler, & Doss, 1992; Urry et al., 2004). However, although growth reports were related to positive affect, it was shown in chapter 3.3 that the correlation of PTG and brain asymmetry remained significant after positive affect was statistically controlled.

A second link between PTG and anterior brain asymmetry may be coping. On the one hand, as reviewed in chapter 2.8 it is widely acknowledged that coping with trauma represents a central mechanism for achieving growth as an outcome. Furthermore, PTG when viewed as a process may be a coping mechanism itself (for discussion see also Park & Helgeson, 2006; Zoellner & Maercker, 2006b). Empirically, self reported growth has been associated with several coping mechanisms such as positive reinterpretation coping (Frazier et al., 2009; Sears, Stanton, & Danoff-Burg, 2003; Siegel, Schrimshaw, & Pretter, 2005) but also with acceptance coping and denial (see reviews Helgeson et al., 2006; Zoellner & Maercker, 2006b). A possible link to EEG asymmetry research may be findings that trait-like relative left hemisphere activity is associated with a positive affective style which means a tendency to react rather positive to emotion-elicitors. Furthermore, left hemisphere activity has been linked with positive emotion-regulation (Jackson et al., 2003), positive reappraisal (Ochsner et al., 2002), as well as a self enhancing coping style called repression or defensiveness (Kline et al., 1998; Tomarken & Davidson, 1994). This partly self-deceptive coping style has been associated with self-enhancing cognitive and regulatory processes (Tomarken & Davidson, 1994), and lower risk for depression (Lane, Merikangas, Schwartz, Huang, & Prusoff, 1990). Thus, the theoretical association of repressive coping and PTG, which both are associated with anterior asymmetry, might explain the relation of growth and distress. As discussed in chapter 3.3.4 however, research is necessary to more directly assess the relation between PTG, resting frontal asymmetry and its associated self-regulatory mechanisms. At this point its noteworthy that EEG asymmetry can not be viewed as a mechanism itself, but rather, as a marker of some underlying neural process (Cacioppo, 2004). Given the sizable literature, EEG asymmetry research has established a great psychological construct validity as a measure of an underlying approach-related or withdrawal-related motivational style and emotions (Coan & Allen, 2004). Thus, the connection of EEG asymmetry and growth may help to increase construct validity of PTG. Altogether, as reviewed in chapter 2.8 there are many basic questions to be answered regarding validity, conceptualization, and assessment of PTG and its relations with adjustment and well-being.

4.4 The relation of measures of brain function and psychotherapy

One important area for future works concerns the neuroscientific investigation of psychological treatment in general (Etkin, Pittenger, Polan, & Kandel, 2005; Moras, 2006)

and especially in PTSD (Peres, McFarlane, Nasello, & Moores, 2008). Even before the area of neuroimaging, it was suggested by Freud 1895 (Freud, 1950) that changes in affect, cognition, and behavior due to psychotherapy are mediated by the so called “in between” the brain. Nobel Prize winner Eric Kandel (1998) more directly suggested, “that all mental processes, even the most complex psychological processes, derive from operations of the brain“ (p.460) and changes in the patients mind due to psychotherapy should be related to changes in the patients brain.

In this view neuroscience has been suggested to be useful to psychotherapy in several ways: to help to understand mechanisms underlying the development and maintenance of the psychological disorder; for the validation of existing psychotherapeutic theories and interventions; for the understanding of change mechanisms of efficacious psychological treatments and therefore for the development of more efficient psychological therapies (Cappas, Andres-Hyman, & Davidson, 2005; Moras, 2006; van der Kolk, 2006).

Several possible directions for further research on the question how psychotherapy is related to brain mechanisms are imaginable. First, one of the most important questions of psychotherapy research is what the mechanisms of change due to treatment are (Moras, 2006). For CBT of PTSD, there are several mechanisms postulated to underlie successful treatment as: reduction of avoidance, habituation, cognitive reappraisal, elaboration of autobiographical memory or integration of competing memories (Brewin, 2008; Ehlers & Clark, 2000; Foa, 1997). As suggested in chapter 3.2.4 one possibility in what measures of brain activity might help to disentangle the specific effects of various intervention strategies would be to compare changes of brain function of different psychological treatment components for PTSD: e.g. cognitive restructuring, different kinds of exposure, relaxation training, stress management, imaginary rescripting or combinations of these interventions. Furthermore, it might be interesting to compare the effects of different psychological treatments with medication or combinations of both on measures of brain activity in PTSD. To date, there are no such studies for PTSD but for depression (Goldapple et al., 2004) and social phobia (Furmark et al., 2002), suggesting that clinical recovery due to psychological or pharmacological treatment seems to have some common but also different neural correlates.

A possibility to increase treatment efficacy in future might be to predict treatment response based on neurobiological profiles. For example, in a recent meta-analysis, Seminowicz et al. (2004) investigated the differential effects of psychotherapy and medication. They found that categorization of types of depression based on neural responses

may differentiate responders and non-responders of medication and psychotherapy and thus may increase treatment efficacy. For PTSD, preliminary evidence suggests that structural (Bryant, Felmingham, Whitford et al., 2008) and functional (Bryant, Felmingham, Kemp et al., 2008) neuroimaging measures may provide critical information for predicting response to CBT. Given the association of EEG asymmetry and PTSD and its successful treatment (study I and II) and studies showing the predictive value of EEG asymmetry for antidepressive treatments (e.g. Bruder et al., 2008; Bruder, Stewart, McGrath, Deliyannides, & Quitkin, 2004; Bruder, Tenke, Stewart, McGrath, & Quitkin, 1999), a goal of future studies might be to investigate the predictive value of this measure for psychological treatment.

A further field of investigation would be the link of neural mechanisms and general and specific mechanisms of different kinds of psychotherapy for PTSD. There is an ongoing debate that different kinds of psychotherapeutic approaches are associated with general mechanisms of change (Grawe, 2000, 2004; Greenberg & Pascual-Leone, 2006; Imel & Wampold, 2008; Kazdin, 2008; Wampold, 2001). As reviewed in chapter 2.6.2, for PTSD there have been similar patterns of CBF alterations following different treatments (CBT, EMDR, brief eclectic psychotherapy). For example, the results of our study II (using CBT), the study of Lindauer et al. (2008) (using brief eclectic psychotherapy), and the study of Lansing et al. (2005) (using EMDR) found a reduction of activation in right frontal regions after therapy. Other studies (Lansing et al., 2005; Lindauer et al., 2008; Peres et al., 2007) reported a common pattern of increase in left hemisphere cortical regions in response to different psychological treatments for PTSD (brief eclectic psychotherapy, EMDR, CBT). This common pattern of alterations in brain activity due to diverse psychological treatments suggests some common mechanisms of change, despite different theoretical approaches of these treatments. This might in part explain the fact, that for PTSD several psychological treatments have been shown to be effective to reduce symptoms (Benish, Imel, & Wampold, 2008; Bisson & Andrew, 2007).

From a more theoretical perspective, the link between EEG asymmetry research and research of general psychotherapy might be an interesting field for further research. For example, Grawe (2000; 2004) proposed a framework for general psychotherapy based on its “Konsistenztheorie” in which motivational goals: as approach goals and avoidance goals (its conflicts with each other and with reality) are central for development and treatment of psychological disorders. Given the manifest similarity to the approach-withdrawal model of Davidson (see chapter 2.9.3), studies linking these two theoretical approaches are of unique

interest. For example, it would be interesting whether treatments intending a reduction of avoidance goals or an increase of approach goals due to therapeutic interventions are associated with changes in frontal asymmetry.

An further important question for neurobiological research of psychotherapy is: Do we really measure mechanisms of change when we compare pre and post assessments of brain activity? It is possible that one measures the outcome of treatment rather than a specific mechanism (Roffman et al., 2005). Thus, it might be useful to assess brain activity during multiple points of time during a treatment protocol: e.g. after each session, or even during treatment sessions, or at follow up. For this kind of research especially the EEG as research tool seems to be well suited. In contrast to the more invasive and expensive measures as PET or MRI, the EEG is a relatively noninvasive, inexpensive and even portable measure of cortical activity (Davidson, Jackson et al., 2000). Furthermore, in such a design a combination with psychophysiological research measures might be useful to compare different levels of change (behavioral, physiological, and neural). This kind of research could also be helpful for answering questions regarding optimal length of treatment protocol and session as well as optimal time between sessions.

There are several methodological problems associated with the measurement of neural correlates of psychotherapy of PTSD. First, as reviewed in chapter 2.6.1., there are several general methodological problems of earlier studies of brain function in PTSD which may influence results and complicate comparisons of different studies. Such factors are: method of measurement of brain activity (e.g. fMRI, PET, SPECT, EEG), type of trauma, comorbidity, current medication, dominant symptoms (e.g. intrusions, numbing, avoidance), or dominant emotions elicited by trauma reminders (e.g. anxiety, anger, guilt, shame). Therefore, comparative research strategies (e.g. the comparison of different imaging techniques in one sample of subjects, or the comparison of different subgroups of PTSD subjects) could help to disentangle the common and distinct effects of these methodological variations. Furthermore, neuroimaging research on PTSD and non-PTSD individuals also might assess individuals in the immediate aftermath of a traumatic event, which might avoid some confounds of assessment of chronic PTSD (e.g. medication history and alcohol abuse).

It is also necessary to compare different groups of psychological disorders and PTSD to demonstrate if findings of brain alterations are specific to PTSD. Furthermore, research regarding the conceptualization of PTSD is necessary to increase validity of the PTSD concept (McNally, 2003; Rosen & Lilienfeld, 2008).

Especially for psychotherapy research, the paradigm used during measurement of brain activity clearly will influence the results. For example, Peres et al. (2007) reported a post-therapy increase in left hemisphere function using a script-driven paradigm in which the subject is instructed to read aloud about the traumatic event. It is logical that this paradigm involves verbal activity which depends on left hemisphere function. In contrast, our study (for details of the procedure see chapters 3.1.2 and 3.2.2) used standardized pictures with no necessary verbal response found a reduction in right hemisphere activation after CBT. Thus, although the direction of changed asymmetry was similar in both studies, differences in experimental paradigms may have a great impact on the observed results and may explain some inconsistent findings of treatment related changes in PTSD (see chapter 2.6.2). Future studies should compare the effects of different paradigms (symptom provocation, baseline) which may increase validity of the results. At last, it is necessary to note that several other methodological variables are probable to influence results of studies of psychological treatment as: number of sessions, amount of therapists, therapeutic setting (group vs. individual therapy) (Dougherty, Rauch, & Rosenbaum, 2004; Roffman et al., 2005).

5 References

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Erklärung gemäß §5 (1) Punkt 5 der Promotionsordnung der Fakultät Mathematik und Naturwissenschaften der Technischen Universität Dresden

Die vorliegende Arbeit „EEG Asymmetries in Survivors of Severe Motor Accidents: Association with Posttraumatic Stress Disorder and its Treatment as well as Posttraumatic Growth“ wurde an der Professur für Biopsychologie im Fachbereich Psychologie der Technischen Universität Dresden unter der Betreuung von Prof. Clemens Kirschbaum und Dr. Anke Karl angefertigt.

Hiermit versichere ich, dass ich die vorliegende Arbeit ohne unzulässige Hilfe Dritter und ohne Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe; die aus fremden Quellen direkt oder indirekt übernommenen Gedanken sind als solche kenntlich gemacht. Die Arbeit wurde bisher weder im Inland noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde vorgelegt.

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