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Emotional Instability in Borderline Personality Disorder

Evidence for Disturbances in the Processing and Regulation of Emotions

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Theoretical Background

Chapter 1

The introduction of this thesis will start with an outline of the symptomatology and epidemiology of Borderline Personality Disorder (BPD), followed by a description of the crucial role of emotional instability for the understanding of this severe mental disorder and the relation to several symptoms of BPD. In particular, it will be discussed that emotional instability and the difficulties patients' experience in their everyday life might be a result of enhanced emotional responding and deficits in the regulation of emotions.

Next, a theoretical model of emotion and emotion regulation is described, with the aim to provide a greater framework for the understanding of patients' difficulties in the processing and regulation of negative emotions. The neural representation of emotion and emotion regulation is the topic of the next section.

Subsequently, recent empirical evidence for alterations in the processing and regulation of emotions in patients with BPD will be summarized. Finally, the research questions of this thesis will be outlined.

Borderline Personality Disorder

Borderline Personality Disorder affects up to 6% of the western adult population (Grant, et al., 2008; Lenzenweger, Lane, Loranger, & Kessler, 2007) and is characterized by a pervasive pattern of instability in four domains: affect, behavior, interpersonal relationships, and self-identity (2000). Moreover, self-injurious behavior, dissociation, impulsive aggression, and chronic suicidal tendencies are the most prominent clinical symptoms with severe effects on BPD patients and their social environment (Lieb, Zanarini, Schmahl, Linehan, & Bohus, 2004). The characteristic symptom pattern of BPD patients is associated with pronounced deficits in psychosocial functioning. BPD patients describe severe impairments, even in comparison to patients with mood or other personality disorders (e.g., Ansell, Sanislow, McGlashan, & Grilo, 2007; Skodol, et al., 2002). As a result, patients with BPD feature an extensive use of psychiatric and non-psychiatric treatment utilization (Ansell, et al., 2007; Bender, et al., 2001; Zanarini, Frankenburg, Khera, & Bleichmar, 2001). BPD is typically the most prevalent personality disorder in psychiatric in- and outpatient samples (Grilo, et al., 1998; Korzekwa, Dell, Links, Thabane, & Webb, 2008; Marinangeli, et al., 2000). It was estimated that the treatment of patients with BPD accounts for about 30% of the total costs spent for psychiatric inpatient care in Germany (Bohus & Schmahl, 2007).

Furthermore, clinical studies and manuals suggest a 3:1 female to male gender ratio (2000). However, increased rates of female BPD patients observed in clinical settings might be explained by differences in treatment seeking behavior, and diagnostic biases due the clinical presentation and gender-specific differences in co-morbid disorders (Skodol & Bender, 2003). For instance, female patients with BPD are more likely to meet diagnostic criteria for eating disorders and post-traumatic stress disorder, whereas higher rates of substance abuse disorders and antisocial personality disorder are reported in male patients with BPD (D. M. Johnson, et al., 2003; Zanarini, et al., 1998; Zanarini, et al., 1999). Accordingly, and in contrast to clinical settings, most epidemiologic studies have failed to report gender specific differences in the occurrence of BPD in the general population (Coid,

Yang, Tyrer, Roberts, & Ullrich, 2006; Grant, et al., 2008; Lenzenweger, et al., 2007; Torgersen, Kringlen, & Cramer, 2001). Importantly, BPD is also highly prevalent in forensic institutions and prisons (Coid, et al., 2006; Sansone & Sansone, 2009). Patients with BPD are at elevated risk for violent behavior, especially for impulsive aggression in the context of interpersonal rejection (Fountoulakis, Leucht, & Kaprinis, 2008; Porcerelli, Cogan, & Hibbard, 2004). Thus, they are more likely to have a criminal conviction and to have spent time in prison.

The high prevalence and severe impairments of patients with BPD highlight the need to provide adequate treatment options, which represents a major challenge for the Healthcare System standing alone, but furthermore stresses the necessity for a better understanding of this severe mental disorder to advance current treatment approaches.

Emotional Instability – A Key Feature of BPD

Affective instability is consistently found to be the most frequent and stable diagnostic criterion in BPD (Glenn & Klonsky, 2009; Lieb, et al., 2004; McGlashan, et al., 2005; Trull, et al., 2008). For this reason, affective instability is considered to be the most characteristic feature of BPD (Linehan, 1993, 1995) and to be "at the core of borderline pathology" (Stiglmayr, et al., 2005, p. 372). The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) defines the criterion of affective instability in BPD as "due to a marked reactivity of mood (e.g., intense episodic dysphoria, irritability, or anxiety usually lasting a few hours and only rarely more than a few days)" (p.654). The glossary of the DSM-IV-TR additionally states that affective lability is further characterized by an "abnormal variability in affect with repeated, rapid and abrupt shifts in affective expression" (p.763). Accordingly, patients with BPD describe more frequent, stronger, and longer-lasting states of aversive emotional states (Ebner-Priemer, et al., 2007; Stiglmayr, et al., 2005; Stiglmayr, Shapiro, Stieglitz, Limberger, & Bohus, 2001).

In contrast to the provided diagnostic definitions of the DSM-IV, I will use the term *emotional instability* during the course of this thesis. Although the terms *affect* and *emotion* are used interchangeably by a great number of people and also scientific researchers, both terms represent nonetheless no synonyms. Emotions represent specific states that are elicited in certain situations or by certain stimuli that are relevant for the goals or well-being of the individual (a detailed definition will be provided in the next section), whereas affect rather represents a higher-level category that includes different subjective states such as moods, impulses, emotions and stress responses (Scherer, 1984). In the context of this thesis, the term emotional instability is more appropriate as the overwhelming majority of empirical research in BPD investigated the effects of mainly negative stimuli that are proposed to elicit emotional responses.

Remarkably, most symptoms in BPD are proposed to be directly related to emotional instability. For instance, the majority of patients with BPD show several forms of self-injurious behavior, such as burning or cutting. Empirical studies estimated that up to 90% of BPD patients engage in deliberate self-injurious behavior (Skodol, et al., 2002; Zanarini, et al., 2008). The self-inflicted pain seen in BPD patients might be directly related to emotional instability. In particular, it was proposed that self-injurious behavior reflects a dysfunctional attempt to deal with aversive emotional states (Klonsky, 2007; Niedtfeld & Schmahl, 2009). In line with this conceptualization, BPD patients report to use self-injury to escape from undesired or extreme emotions (Chapman, Gratz, & Brown, 2006; Kleindienst, et al., 2008). Emotional instability was furthermore found to be associated with feelings of chronic emptiness, interpersonal problems, and identity disturbances (Koenigsberg, et al., 2001; Tragesser, Solhan, Schwartz-Mette, & Trull, 2007). Additionally, some authors argue that impulsive behavior also represents a dysfunctional attempt to cope with negative emotional states, thereby again emphasizing the fundamental role of emotional instability for the understanding of BPD psychopathology. However, other authors pointed out that impulsive behavior is independent of emotional instability and only the combination of both factors explains the psychopathology in BPD patients (for a discussion of emotional instability and impulsivity, see Tragesser & Robinson, 2009). Thus, to date, the specific relation between emotional instability and impulsivity is still unsettled.

Emotional instability is hypothesized to be a result of both enhanced emotional reactivity and the inability to control intense negative emotional states. Earlier conceptualizations proposed that enhanced emotional sensitivity, for example to facial expressions of emotions, might be a third factor underlying emotional instability in BPD (Linehan, 1993). However, behavioral results in this domain contradict the assumption of a general hypersensitivity to facial expressions rather illustrating subtle impairments in basic emotion recognition and more negative interpretations of ambiguous expressions (for a review, see Domes, Schulze, & Herpertz, 2009). In line with two-factorial theories of emotional instability, models of temperament report high negative emotionality and low

volitional control in BPD (Posner, et al., 2002; Posner, et al., 2003). Concurrently, two-dimensional models of social adult attachment reported more extreme emotional reactivity and difficulties in cognitive control and executive functioning in BPD (Minzenberg, Poole, & Vinogradov, 2006, 2008). It might be additionally fruitful to investigate deviant processing of emotions as well as deficits in emotion regulation to improve the understanding of the observed impairments in the recognition of facial emotional expression in BPD. Both processes were proposed to interfere with the recognition of mental states and facial expressions (Domes, et al., 2009; Wolff, Stiglmayr, Bretz, Lammers, & Auckenthaler, 2007). Possibly, a similar mechanism might account for difficulties in the recognition of thoughts and intentions of other people in everyday-life situations (Preissler, Dziobek, Ritter, Heekeren, & Roepke, 2010).

Taken together, emotional instability is central for the understanding of BPD and directly related to many aspects of BPD psychopathology. Both, stronger emotional responding and pronounced deficits in the regulation of negative emotions are thought to underlie emotional instability in BPD. The crucial role of emotional instability is further emphasized in the currently most common treatment approach – Dialectical Behavior Therapy (DBT). This cognitive-behavioral treatment primarily aims to provide patients with techniques supporting the regulation of aversive emotional states (Linehan, 1995). For instance, patients learn to identify and label their emotion, to change their emotions, or to use distress tolerance techniques. A recent meta-analysis supports the efficacy of DBT for the treatment of patients with BPD (Kliem, Kroger, & Kosfelder, 2010). The encouraging short-term results of DBT underline the necessity to focus on emotional instability with regard to theoretical and therapeutic concepts in patients with BPD.

A Framework of Emotion and Emotion Regulation

The following section primarily aims to outline the conceptual framework of James Gross' model of emotion regulation (Gross, 1998a, 1998b, 2002; Gross & Thompson, 2007; Ochsner & Gross, 2005). The ability to regulate negative emotions is crucial for successful social interactions, mental health and psychological well-being (Davidson, 2000; Eftekhari, Zoellner, & Vigil, 2009; Gross & John, 2003). The section will start with a definition of the term emotion that forms the theoretical basis of this model. In this way, the section provides the reader with a current model of emotion and emotion regulation to allow for a more appropriate classification of BPD patients' difficulties.

Each attempt to define and investigate emotion regulation is immediately confronted with the task to provide an answer to the urgent question of "what is being regulated" (Gross & Thompson, 2007, p. 4). For that reason, a framework of emotion regulation has to start with a definition of emotion. This task has proven to be difficult in the past and is additionally complicated by a synonymous use of different words in common speech, such as affect and emotion (see previous section). Nonetheless, there are three relatively undisputed features that form the *modal model* of emotion and represent the theoretical basis of recent frameworks of emotion regulation (Gross & Thompson, 2007). Firstly, emotions are elicited in light of an attended situation, or stimulus, that is relevant to the person's goals, values, or well-being. The individual appraisal and relevance of the situation is extremely important for the development of an emotion. For example, the breaking news report of a devastating earthquake in South America might elicit strong emotions of fear or sadness (depending on the magnitude of the earthquake), especially in persons with friends or relatives in this region. Secondly, emotions involve changes in various components such as cognition, physiological states, or subjective experience. When confronted with the news, persons would possibly show an enhanced level of physiological arousal or would start to tremble. The third feature is known as control precedence and describes the fact that "emotions in general tend to assume precedence in the control of action and attention" (Frijda, 2007, p.

28). In other words, emotions have a quality that might overtake our behavior and thinking. To remain with the preceding example, until the affected persons were able to get in touch with their friends or relatives, they will repeatedly attempt to establish telephonic contact, and their thoughts are overrun by worries.

The features of the emotion generation process were further simplified in a temporal sequence that is illustrated in Figure 1.1 (Gross & Thompson, 2007). The starting point is an either external or internal situation, which is attended to and subsequently appraised in terms of personal relevance or valence. Importantly, it is the appraisal of the situation, and not the characteristics of the situation, that is crucial for the development of an emotion. The same situation might be appraised in distinct ways and could therefore lead to different emotional responses (Siemer, Mauss, & Gross, 2007). As described above, the emotional response itself changes subjective experiences, cognitions, and bodily states. Additionally, the authors proposed that the emotional response may recursively affect the situation, thereby resulting in a change of appraisal and the subsequent emotional responses.

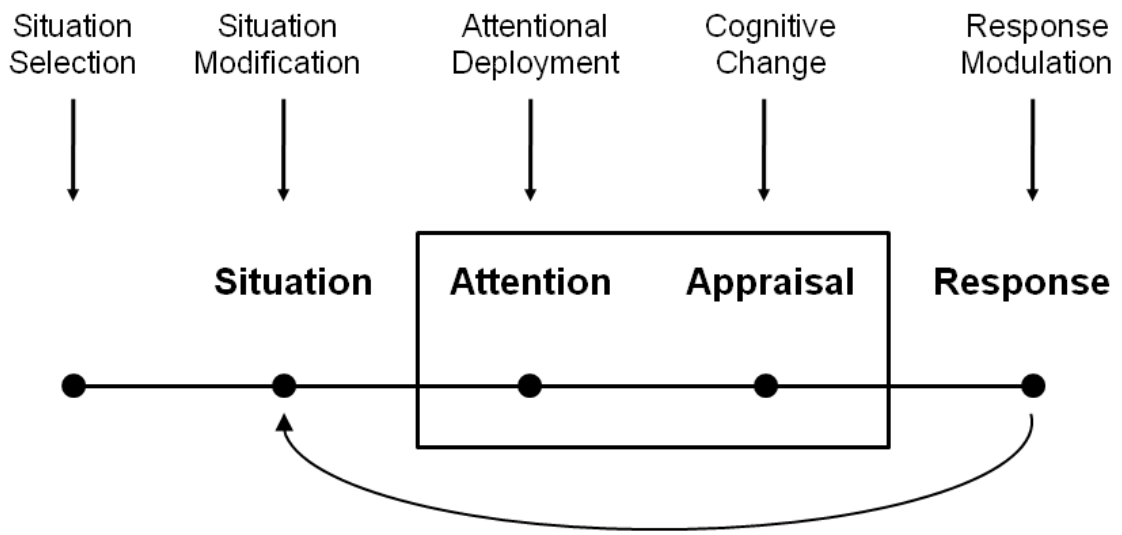

Figure 1.1. **Process model of emotion generation and emotion regulation.** (reproduced from Gross & Thompson, 2007, p.10)

In an influential review article by James Gross (1998b), the concept of emotion regulation was directly associated to the temporal sequence of emotion generation and defined as follows:

> *Emotion regulation* refers to the processes by which individuals influence which emotions they have, when they have them, and how they experience these emotions. Emotion regulatory processes may be automatic or controlled, conscious or unconscious, and may have their effects at one or more points in the emotion generative process […] Because emotions are multicomponential processes that unfold over time, emotion regulation involves changes in 'emotion dynamics' (Thompson, 1990), or the latency, rise time, magnitude, duration, and offset of responses in behavioral, experiential, or physiological domains. (p. 275)

The definition proposes a process model of emotion regulation, therefore the regulation strategies directly refer to the time course of emotion generation as described by the modal model of emotion (for a theoretical discussion if emotion generation and emotion regulation

can be distinguished, see Gross & Barrett, 2011). At the broadest level, emotion regulation can be differentiated into *antecedent-focused* and *response-focused* strategies, illustrating that these strategies are deployed either before or after an emotional response is generated (Gross, 1998a, 1998b, 2002; Gross & Thompson, 2007). More precisely, five classes of regulatory strategies were suggested that differ by the time point at which they have their key impact in the emotion generative process. These five sets of emotion regulation strategies are termed *situation selection*, *situation modification*, *attentional deployment*, *cognitive change*, and *response modulation* (Gross, 1998a, 1998b, 2002; Gross & Thompson, 2007). The respective time points in the emotion generative process targeted by these five sets of strategies are illustrated in Figure 1.1.

The strategies summarized as situation selection refer to “approaching or avoiding certain people, places, or things so as to regulate emotions” (Gross, 2002, p. 282). These strategies involve anticipation processes and a complex balancing of short- and long-term emotional responses. For instance, one might be invited to a party that the former partner (after a dramatic breakup a couple of weeks ago) is supposed to attend with her/his new partner. If the anticipated anguish is too much to handle, one might decide to stay at home or go somewhere else that evening. Although it is sometimes preferable to avoid situations, some individuals tend to overemphasize short-term emotions, thereby enhancing negative emotions in the long-term. Socially anxious individuals, for instance, are known to favor the avoidance of a fear-eliciting situation such as peer-evaluation, thereby further restricting social interactions in turn (*Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR*, 2000).

Nevertheless, even though negative emotional responses are anticipated (e.g., anger, sadness), one might decide to go to the party. However, to weaken the pain of seeing a former loved person with her/his new partner, one might try to alter the situation of attending the party. Situation modification strategies consequently refer to the fact that “a situation may be tailored so as to modify its emotional impact “ (Gross, 2002, p. 283). Instead of going alone, one might call some friends to ensure that they will be at the party too (to not be alone

when finally seeing the new couple for the first time), or one might “hide” in the kitchen to prevent physical proximity and to not have to engage in a conversation.

Furthermore, attentional deployment is defined to be “used to select which of the many aspects of the situation you focus on” (Gross, 2002, p. 283). Each situation comprises various aspects that substantially differ in their ability to elicit emotions. For that reason, a change of one’s attentional focus is capable to regulate emotions. At the party, for instance, one might engage in an ongoing conversation or in a competitive match of table football to not have to see the former love interest (in the worst kissing) with her/his new partner. Attentional deployment is also assumed to be the first emotion regulation strategy that children develop. A shift of gaze, away from the emotion generative stimuli, is typically observed in infants. In addition, it is often seen that people cover their ears or close their eyes in emotionally arousing situations. In emotion regulation terms, they withdraw their attentional resources and restrict further elaborate processing of the situation, consequently altering the intensity of the emotional response (for a thorough discussion of developmental aspects of emotion regulation, see Calkins & Hill, 2007; Charles & Carstensen, 2007; Holodynski & Friedlmeier, 2005; Stegge & Terwogt, 2007). The major strategies of attentional deployment are attentional selection, distraction, and concentration (Gross, 2002; Gross & Thompson, 2007; Ochsner & Gross, 2005).

As pointed out above, the attentional selection of a situational aspect is closely associated with the subsequent appraisal. However, the selected aspect does not automatically involve a predefined appraisal. For that reason, cognitive change is defined as “selecting which of the many possible meanings […] you will attach to that aspect” (Gross, 2002, p. 283). Presumably, a change of the situational appraisal transforms the emotional response. The direction of this emotion transformation depends on the selected appraisal. The mechanism of cognitive change is mostly used to decrease the intensity of negative emotions, but can be additionally used to increase the intensity of emotions (e.g., of positive emotions). The term "cognitive reappraisal" refers to a strategy that is used to change the

initial appraisal of the situation and has gained growing research interest in recent years. The interest in reappraisal might be due to the fact that it represents an emotion regulation strategy commonly applied in cognitive-behavioral therapy. In these settings, patients are frequently taught to critically evaluate their initial appraisals and to re-appraise the situation. The psychological mechanisms of cognitive reappraisal clearly differ from distraction processes (Gross & Thompson, 2007). During cognitively reappraising an emotion-eliciting situation, the attentional focus remains on the stimulus, whereas during cognitive distraction the attentional resources are drawn from the emotion-eliciting situation and are absorbed by the performance of an additional task.

Finally, emotion regulation might also occur after the emotional response is already generated and thereby aims to modulate emotional responses. By definition, “response modulation refers to influencing physiological, experiential, or behavioral responding as directly as possible” (Gross & Thompson, 2007, p. 15). Turning back to the previous example, one might attempt to hide the elicited emotions of anger or sadness while watching the former partner with his/her new lover by restricting the facial expressions of these emotions. In everyday life, the suppression of expressing emotions is typically applied in situations that one is not able to change, such as working contexts. At work, most people experience more negative emotions than in their private lives (e.g., Stone, et al., 2006), along with a tendency to suppress the expression of these negative emotions (Diefendorff & Greguras, 2009; for further discussions of emotion and emotion regulation in organizational contexts, see Grandey & Brauburger, 2002; Hochschild, 2003). It is important to note that the suppression of emotional responses (for instance of facial emotional expressions, as famously illustrated in games of poker) does not result in a change of the emotional intensity, in contrast to antecedent-focused strategies. In addition, emotion suppression was found to disrupt memory processes and to impair the quality of social interactions compared to cognitive reappraisal (Butler, et al., 2003; Egloff, Schmukle, Burns, & Schwerdtfeger, 2006; Richards & Gross, 2000). For that reason, it was previously suggested that suppression

might have more negative effects on mental health and well-being than cognitive reappraisal (for a discussion, see John & Gross, 2004).

This section aimed to illustrate the temporal dynamics of the generation of emotions and associated regulatory strategies that either alter the intensity of an emotion or initiate a new emotional response (antecedent-focused strategies), or the expression of the emotional response (response-focused strategies). How the brain implements the processing and regulation of emotions is topic of the next section, where recent findings will be briefly summarized.

Neural Networks of Emotion and Emotion Regulation

The beginning of this section will provide a short illustration of the role of the amygdala and the insula in the processing of emotions in general. Both structures are proposed to be key components in the representation of emotions. This will be followed by a description of the neural networks of the cognitive control of emotions. The focus will be particularly on attentional deployment and cognitive reappraisal, since both strategies were investigated in the studies presented in Chapter 2, 3, and 4.

The processing of emotions is strongly associated with the almond-shaped structure of the amygdala, localized in the anterior medial temporal lobe. The amygdala is part of the limbic system, which additionally comprises the thalamus, and ventral parts of the anterior cingulate cortex, the medial prefrontal cortex and the striatum (Alexander, Crutcher, & DeLong, 1990). Indeed, the amygdala plays a crucial role in the processing of emotional stimuli. Although initially thought to be primarily involved in processing of fearful facial stimuli (Morris, et al., 1996; Whalen, et al., 2001), recent evidence rather suggests a general role of the amygdala in the processing of emotional stimuli (e.g., Costafreda, Brammer, David, & Fu, 2008; Kober, et al., 2008; Phan, Wager, Taylor, & Liberzon, 2004). Apart from dense connections with visual cortices (Amaral, Behniea, & Kelly, 2003), the amygdala conveys additional information by a subcortical route - via the superior colliculus (Vuilleumier & Pourtois, 2007), especially in cases of unawareness of emotional stimuli (Morris, Ohman, & Dolan, 1998; Whalen, et al., 2004; Whalen, et al., 1998). Nevertheless, emotion processing cannot be solely attributed to the amygdala. The importance of several additional neural structures is highlighted in the schematic overview presented in Figure 1.2, which illustrates the temporal neurofunctional pattern of facial emotion processing. In addition, recent publications extend the role of the amygdala and propose that this structure might be part of a neural network more generally involved in the detection and processing of behaviorally relevant and salient stimuli (Ousdal, et al., 2008; Pessoa & Adolphs, 2010; Sander, Grafman, & Zalla, 2003; Santos, Mier, Kirsch, & Meyer-Lindenberg, 2011).

Additionally, the insular cortex is of further interest, being part of the paralimbic system and topographically divided into an anterior and a posterior part (Ture, Yasargil, Al-Mefty, & Yasargil, 1999). The insula has widespread anatomic connections to somatosensory networks, auditory networks and prefrontal structures, and further reciprocal connections to the brainstem and the amygdala (Augustine, 1996; Barbas, Saha, Rempel-Clower, & Ghashghaei, 2003). Neuroimaging studies suggest the insula to be critically involved in the integration of multimodal information, and the presentation of bodily states (Critchley, 2009). Accordingly, activation of the insula was consistently found to be correlated with cardiovascular responding (e.g., Critchley, Corfield, Chandler, Mathias, & Dolan, 2000; Critchley, et al., 2005). The insula is additionally broadly involved in the processing of aversive emotions (Meriau, et al., 2009; Straube & Miltner, 2011), especially in disgust (Phillips, et al., 1997; Wicker, et al., 2003).

Interestingly, it was specifically suggested that the insular cortex might represent a neurobiological correlate of "how we feel" (Craig, 2002). This suggestion directly concurs with a theoretical distinction of e*motions* and *feelings* provided by Nico Frijda (1986). He proposed that emotions reflect an individual motivational state of action readiness. This state stimulates human behavior, such as to flee in light of a dangerous situation. Feelings, in contrast, refer to the individuals' awareness of emotional processes that occur after the individual handled the situation. The primary focus shifts back from the world outside (the stimuli or event) to the world within ourselves, and then we become aware of our appraisals and action tendencies (Frijda, 2007).

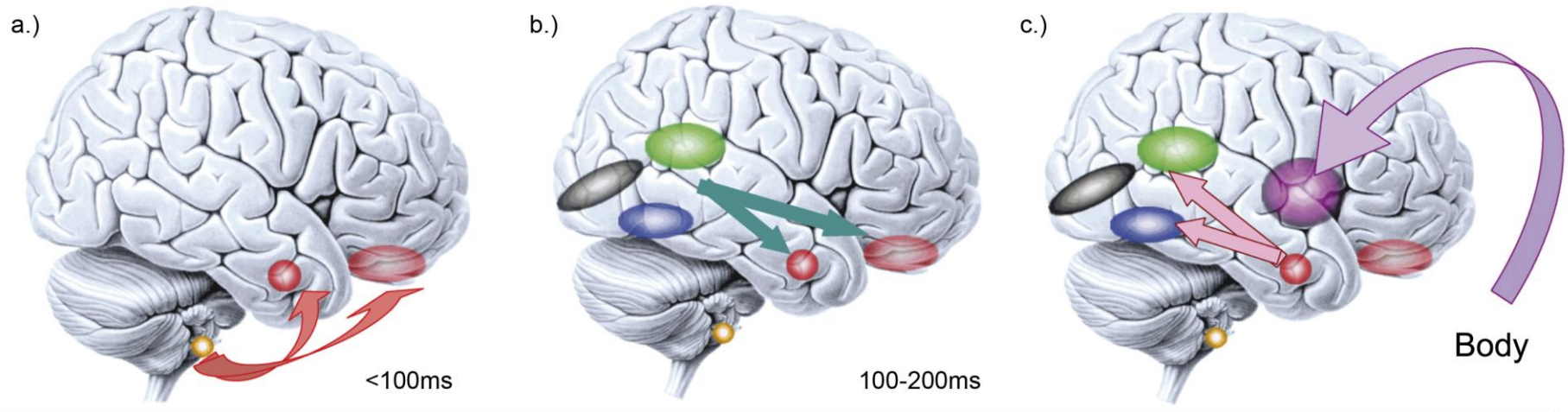

Figure 1.2. **Schematic overview of the temporal neurofunctional pattern of emotion processing illustrated for emotional facial expressions.** a.) Onsets of emotional expressions are accompanied by rapid activations of the orbitofrontal cortex (faint red) and the amygdala (solid red), partially mediated by a subcortical route via the superior colliculus (yellow), the midbrain and the thalamus (Morris, Ohman, & Dolan, 1999; Vuilleumier & Pourtois, 2007). The activation of the amygdala in turn influences visual processing. b.) Subsequently, more detailed input is provided, for example by the fusiform gyrus (blue), which was consistently linked to the processing of static properties of visual stimuli (for a discussion, see Adolphs, 2002), or the superior temporal cortex (green), which is implicated in the processing of dynamic aspects of visual stimuli (Desimone & Ungerleider, 1986; for a critical discussion of the role of the superior temporal cortex, see Hein & Knight, 2008). c.) The result of the stimulus evaluation elicits changes of bodily states (via the medial prefrontal cortex and the amygdala to the brainstem and hypothalamus). Insular structures (purple) are thought to receive continuous updates of individuals' bodily states. (reproduced from Tsuchiya & Adolphs, 2007, p.163)

The neural mechanisms of the cognitive control of emotions have attracted growing research interest in the last years (for reviews, see Ochsner & Gross, 2005, 2007, 2008). Recent studies continue to make great progress in the understanding of the neurobiological correlates underlying a wide range of emotion regulation strategies and the effects of these strategies on emotion processing.

As outlined in the previous section, the focus of attention and the availability of attentional resources are assumed to critically mediate emotion processing. Evidence from visual research paradigms also emphasizes the prominent role of attention. In everyday life we are continuously confronted with a vast number of visual stimuli. Thus, stimuli compete for neural representation and attention processes are proposed to have an essential role to allocate processing resources (Desimone & Duncan, 1995). In line with the *biased competition* account of selective attention, imaging studies illustrated significant interactions between emotion processing and the availability of attentional resources. For instance, Pessoa and colleagues (2005) parametrically varied the attentional demands of a orientation matching task of peripherally presented bars, while centrally presenting neutral, or fearful facial stimuli. A differential activity of the amygdala was only observed during conditions of low task demands. The essential role of selective attention in emotion processing was corroborated by further studies (e.g., Bishop, Jenkins, & Lawrence, 2007; Pessoa, McKenna, Gutierrez, & Ungerleider, 2002; Silvert, et al., 2007). However, other studies suggest that the processing of emotional stimuli is not altered by modulations of attention. Due to their superior behavioral relevance, emotional stimuli might be rather processed automatically (e.g., Anderson, Christoff, Panitz, De Rosa, & Gabrieli, 2003; Glascher, Rose, & Buchel, 2007; Vuilleumier, Armony, Driver, & Dolan, 2001). Correspondingly, specific activations of the amygdala were even found in the absence of visual awareness (Morris, et al., 1998; Whalen, et al., 2004; Whalen, et al., 1998). Thus, to date there is still some controversy regarding the interaction of attention and emotion.

In contrast, cognitive reappraisal was consistently found to modulate neural activity of the amygdala and insula. When subjects are instructed to decrease negative emotions, significant deactivations are observed in the limbic and paralimbic system (e.g., Johnstone, van Reekum, Urry, Kalin, & Davidson, 2007; Ochsner, Bunge, Gross, & Gabrieli, 2002; Urry, et al., 2006). Congruently, the instruction to increase negative emotions resulted in enhanced activations of the emotion processing complex (e.g., Domes, et al., 2010; Eippert, et al., 2007; Ochsner, et al., 2004). Furthermore, the impact of reappraisal on emotions is supported by a widespread prefrontal network (illustrated in Figure 1.3.). There is considerable agreement of the neural regions involved in cognitive reappraisal. In particular, dorso- and ventrolateral, orbitofrontal, medial and anterior cingulate regions as well as parts of the temporo-parietal cortex were consistently implicated (e.g., Domes, et al., 2010; Eippert, et al., 2007; Johnstone, et al., 2007; Ochsner, et al., 2002; Ochsner, et al., 2004). However, the reported localizations of prefrontal regions vary substantially across studies (Ochsner & Gross, 2005). Apart from the use of different reappraisal strategies, two important points might explain the variability in the observations of neural activity. Firstly, experimental paradigms can be subdivided by the time point of the reappraisal instruction relative to the emotion-generative process. In other words, studies either present the instruction prior to the onset of the emotion-eliciting stimulus, or several seconds after the onset of the stimulus. Strictly spoken, studies that present the instruction prior to the onset of the stimulus might not investigate *re*-appraisal but rather *biased* appraisal. Secondly, studies differ in their time periods to implement cognitive reappraisal, from 4 seconds (Ochsner, et al., 2002) to 20 seconds (Harenski & Hamann, 2006). The importance of time considerations in cognitive reappraisal was pointed out in a review that proposed two stages of cognitive reappraisal – early implementation and later maintenance (Kalisch, 2009). Sustained effects of reappraisal on amygdala activity, even after a delay of 15 minutes, were recently reported (Erk, et al., 2011).

Despite a growing body of research publications on emotion regulation, surprisingly less is known about the functional connectivity between structures implicated in emotion

processing and the widespread prefrontal network that underlies cognitive reappraisal. Connectivity analyses suggest that the strength of coupling between the amygdala and the orbitofrontal cortex, as well as between the amygdala and the dorsomedial cortex mediate the success of reappraisal (Banks, Eddy, Angstadt, Nathan, & Phan, 2007). The ventrolateral prefrontal cortex – via a subcortical pathway through the nucleus accumbens – was additionally demonstrated to mediate the decline in negative emotions (Wager, Davidson, Hughes, Lindquist, & Ochsner, 2008).

To recapitulate, the amygdala and insula represent important nodes in a more widespread neural network mediating the processing of emotions. Imaging studies investigating the effects of attention currently provide mixed results. On the one hand, emotional stimuli might be processed automatically and independently of available attentional resources. On the other hand, attentional load was also found to strongly modulate neural responses of the amygdala. Cognitive reappraisal was consistently found to alter emotions in accordance with the regulatory goal as illustrated by activity changes in the amygdala and insula. Effects of cognitive reappraisal are mediated by a prefrontal network, particularly by orbitofrontal and ventrolateral parts of the prefrontal cortex.

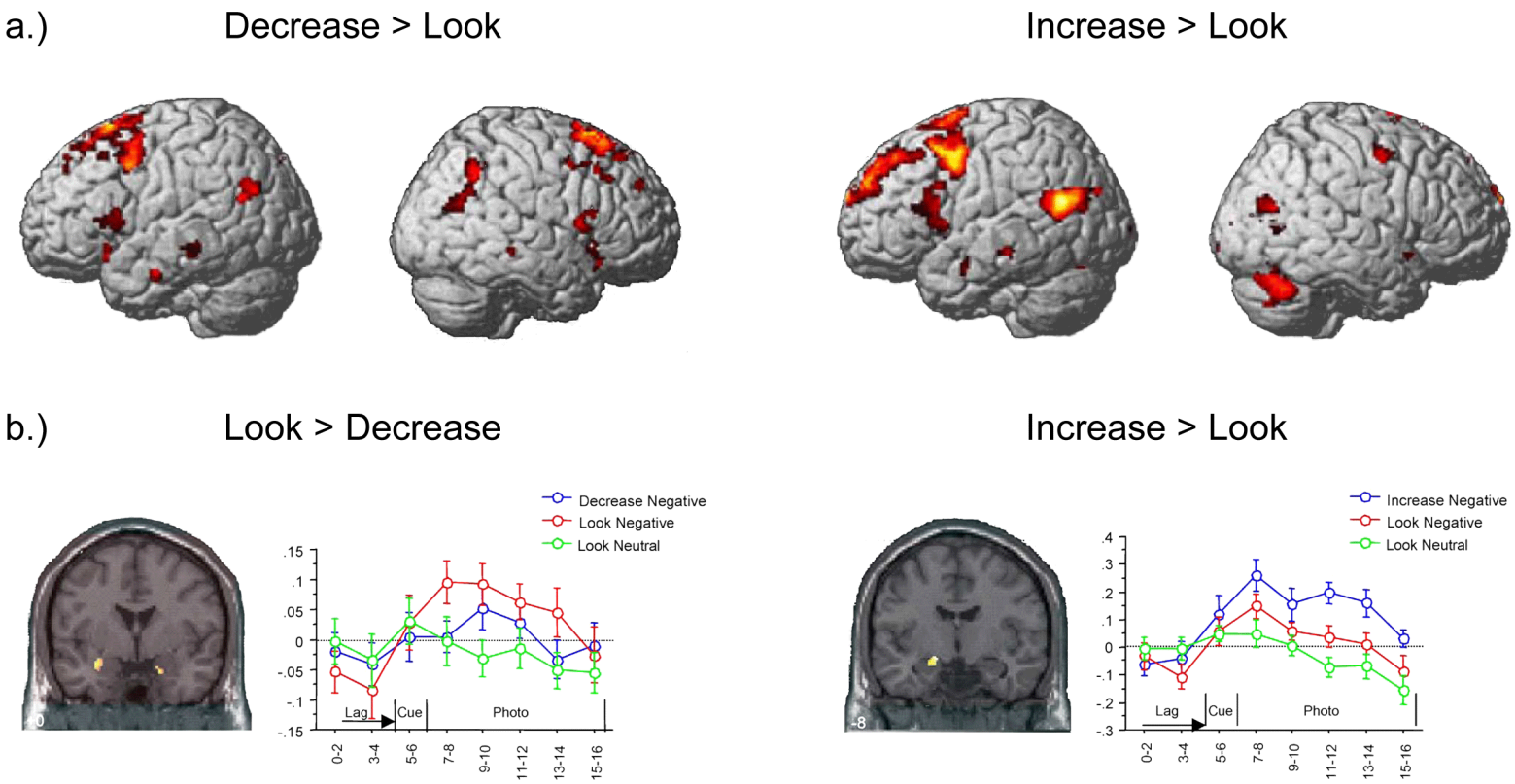

Figure 1.3. **Exemplary illustration of neural patterns associated with cognitive reappraisal.** a.) The decrease of negative emotions enhances neural activations of the bilateral dorsolateral, orbitofrontal and medial prefrontal cortex. Subjects show predominantly left-sided activation of the lateral and medial prefrontal cortex during the increase of emotions. b.) Neural activity of the amygdala showed a decrease or increase in accordance with the regulatory goal. (adapted from Ochsner, et al., 2004)

Empirical Support for Disturbed Processing and Regulation of Emotions in BPD

The key role of emotional instability in the understanding of BPD resulted in numerous studies that used a wide-range of methodological approaches to investigate the processing and regulation of mainly negative emotional stimuli. Analyses of self-report measures consistenly revealed stronger negative responses to emotionally evocative stimuli and greater emotional instability in BPD (for a review, see Rosenthal, et al., 2008). For instance, patients described more intense and more rapid alterations of emotions in response to a short-story (Herpertz, et al., 1997). Behavioral studies suggested attenuated inhibition of negative stimuli (Domes, et al., 2006; Silbersweig, et al., 2007), deficits in attentional disengagement from negative facial expressions (von Ceumern-Lindenstjerna, et al., 2010a) and hypervigilance for emotional cues (Arntz, Appels, & Sieswerda, 2000), especially if associated with BPD-specific cognitive schemas (Sieswerda, Arntz, Mertens, & Vertommen, 2007).

Contrary to theoretical considerations, the first psychophysiological study in BPD provided evidence for hypoarousal, as patients were found to be characterized by significantly lower skin conductance responses to emotional images (Herpertz, Kunert, Schwenger, & Sass, 1999). However, in a second investigation only criminal offenders with psychopathy were characterized by emotional hyporesponsiveness, whereas criminal offenders with BPD did not significantly differ from healthy controls (Herpertz, Werth, et al., 2001). Additional studies provided evidence for hypo- but also hyperarousal in BPD (Ebner-Priemer, et al., 2005; Schmahl, Elzinga, et al., 2004). Two possible explanations were discussed regarding the inconclusive pattern of psychophysiological responding in BPD. Firstly, individuals with BPD are more likely to experience dissociative symptoms (e.g., depersonalization, derealization) during emotionally challenging situations, which might attenuate emotional responding. A study by Ebner-Priemer et al. (2005) examined the influence of present state dissociation on startle responses and highlighted the importance of

present dissociative experiences on psychophysiological responding. Patients with low scores of current dissociation showed emotional hyperarousal. In contrast, BPD patients characterized by high scores of present dissociative experiences were found to show reduced responding. Secondly, personal relevance of the experimental stimuli might influence emotional responding and thereby serve to explain the inconclusive results (Rosenthal, et al., 2008). BPD specific beliefs are particularly characterized by themes of social rejection, such as “loneliness”’ or “unloveability” (Arntz, Dreessen, Schouten, & Weertman, 2004). Patients with BPD are particularly sensitive to rejection, even more than patients with social anxiety disorders (Staebler, Helbing, Rosenbach, & Renneberg, 2010). Experimental research revealed a bias to feel more readily excluded even during equal social participation in a ball-tossing game in BPD. Furthermore, patients displayed additionally more ambiguous facial expressions during social exclusion that might relate to their difficulties in social interactions (Staebler, et al., 2011). In line with the proposed importance of rejection sensitivity, social exclusion was found to represent a highly important trigger for intense states of aversive tension and the urge for self-injurious behavior (Stiglmayr, et al., 2005). A recent study used a script-driven imagery paradigm to investigate patients’ psychophysiological responses to standard (neutral, pleasant, unpleasant), idiographic and disorder-specific scripts (Limberg, Barnow, Freyberger, & Hamm, 2011). The findings suggest that specific scripts containing scenes about rejection and abandonment result in increased startle responses and levels of skin conductance. Congruently, the presentation of negative (and BPD specific) salient words results in enhanced startle responses (Hazlett, et al., 2007).

Early neuroimaging studies were primarily interested in the structural properties of the brain in BPD. The authors found significantly reduced volumes of the bilateral hippocampus and the bilateral amygdala (e.g., Driessen, et al., 2000; Schmahl, Vermetten, Elzinga, & Douglas Bremner, 2003). Subsequent attempts failed in part to replicate reduced amygdalar volume in patients with BPD (e.g., Brambilla, et al., 2004), though these discrepancies might be explained by different co-morbid disorders in BPD patients (Zetzsche, et al., 2006). Two

recent meta-analyses aimed to clarify this point and reported reduced volumes of the bilateral hippocampus and amygdala in BPD (Hall, Olabi, Lawrie, & Mcintosh, 2010; Nunes, et al., 2009). In addition, reduced volumes were found for the orbitofrontal cortex, parts of the dorsolateral prefrontal cortex and the anterior cingulate cortex (e.g., Berlin, Rolls, & Iversen, 2005; Brunner, et al., 2010; Chanen, et al., 2008; Tebartz van Elst, et al., 2003), which is furthermore characterized by diminished interhemispheric structural connectivity (Rüsch, et al., 2010).

Resting-state positron-emission tomography (PET) scans illustrated hypo-metabolism in the anterior cingulate and the orbitofrontal cortex in BPD (De La Fuente, et al., 1997; Soloff, et al., 2003). Moreover, aggressive provocation results in a heightened amygdala metabolism along with an attenuated metabolism in dorsolateral prefrontal regions (New, et al., 2009). Finally, recent PET-results suggest a functional disconnection of prefrontal and limbic regions in BPD (New, et al., 2007).

In response to negative (but also neutral) social scenes and expressions, functional imaging studies consistently found enhanced limbic and paralimbic activity in BPD (Donegan, et al., 2003; Herpertz, Dietrich, et al., 2001; Koenigsberg, Siever, et al., 2009; Minzenberg, Fan, New, Tang, & Siever, 2007; Niedtfeld, et al., 2010). In the context of negative stimuli, patients had difficulties to inhibit behavioral responses in a Stroop and a go-/no-go task (Silbersweig, et al., 2007; Wingenfeld, et al., 2009). This was accompanied by attenuated activations of the anterior cingulate cortex and ventral medial prefrontal cortex including parts of the orbitofrontal cortex. Furthermore, results of a functional neuroimaging study illustrated attenuated activation in dorsolateral and ventrolateral prefrontal cortices when patients with BPD tried to cognitively distance themselves from negative stimuli (Koenigsberg, Fan, et al., 2009). In addition to cognitive distancing, further strategies to regulate negative emotions were investigated in BPD. As previously stated, self-injurious behavior might be best understood as a dysfunctional attempt to regulate states of aversive tension. Correspondingly, painful stimuli were found to result in significant deactivations of limbic activity (Kraus, et al., 2009; Niedtfeld, et al., 2010; Schmahl, et al., 2006). Importantly, the

authors proposed that the effects of painful stimulation on emotion processing might be explained by shifts of the attentional focus. Sensory stimulation might draw attentional resources from the processing of negative emotions and might hereby cause the soothing effects of self-injury in BPD patients.

In sum, recent studies illustrate that patients with BPD are characterized by enhanced emotional reactivity and by impairments in processes broadly associated with the cognitive regulation of emotions. Furthermore, neuroimaging studies suggest that BPD patients exhibit functional, metabolic, and structural alterations in a frontolimbic network, comprising the amygdala, dorsolateral and orbitofrontal cortex as well as the anterior cingulate cortex. In accordance with the role of frontolimbic networks for the processing and regulation of emotions (e.g., Ochsner & Gross, 2005; Phan, et al., 2004), these alterations may represent neurobiological substrates that underlie emotional instability in BPD (Johnson, Hurley, Benkelfat, Herpertz, & Taber, 2003). Further implications of the presented findings and the resulting research questions will be discussed in the next section.

Research Questions

Prior to an outline of the research questions, I will attempt to integrate the current state of research in BPD with the available knowledge about emotion regulation in general. The combination of both research foci may be fruitful to further refine concepts of emotional instability in BPD.

As previously stated, emotional instability is central for the understanding of BPD and proposed to be a combination of stronger emotional responding and deficits in the cognitive regulation of emotions. Recent evidence illustrated that patients with BPD are characterized by enhanced emotional responding. In particular, enhanced activations of the amygdala and insular cortex might underlie alterations in emotional responding. However, most studies focused primarily on the processing of emotions. Thus, significantly fewer studies are available for impairments in the regulation of emotions. For that reason, the studies of this thesis aimed to investigate two different emotion regulation strategies, i.e., attentional deployment and cognitive change, and their neurobiological correlates in BPD. Despite a lack of research, results in BPD might allow to deduce further hypotheses regarding the effects of successful and dysfunctional emotion regulation. Neuroimaging findings in BPD have consistently highlighted functional, metabolic, and structural alterations in a prefrontal network, particularly in parts of the orbitofrontal and ventrolateral prefrontal cortex. Importantly, both structures play a prominent role in cognitive reappraisal and were found to crucially mediate successful reappraisal. For instance, activation of the ventrolateral prefrontal cortex during cognitive reappraisal was found to predict the decline of negative emotions (Wager et al., 2008). Thus, it might be speculated that altered functioning of these prefrontal regions in BPD subserves deficits in cognitive reappraisal. A recent study provided support for weaker effects of cognitive distancing for the regulation of emotions in BPD (Koenigsberg et al., 2009).

Usually it might be further expected that patients with BPD are also impaired in the ability to regulate their emotions via attentional deployment. Deficits in inhibition or attentional disengagement strongly support this view. However, an important module of therapeutic approaches such as DBT is the teaching of strategies to regulate negative emotions via attentional deployment. If patients were not able to implement these strategies, one could assume that therapy evaluations would have provided less encouraging results for DBT in the treatment of BPD. The view of preserved effects of attentional deployment on emotions is further supported by recent findings of pain processing in BPD. Niedtfeld and colleagues (2010) illustrated that the effects of individually adjusted painful sensory stimulation on emotions result in a similar decline of (para)limbic activity. They argued that shifts in the attentional focus might underlie the comparable decrease in negative emotions.

The following studies consequently aimed to clarify the raised questions about cognitive reappraisal and attentional deployment in BPD. Thus, the presented studies aimed to further differentiate patients' difficulties in the regulation of negative emotions and enhance the current knowledge about alterations in emotion regulation processes in BPD.

Study 1 dealt with the effects of cognitive reappraisal on elicited negative emotions in female patients with BPD. Participants underwent functional imaging during a delayed reappraisal paradigm to distinguish between emotional reactivity to a negative stimulus and the subsequent modulation of this response by cognitive reappraisal – in the sense of reinterpretation (Jackson, et al., 2000). The use of a delayed reappraisal paradigm consequently extends a recent report of deficits in the use of cognitive distancing by Koenigsberg et al. (2009). In addition, the experimental design did not only include a decrease condition, but also the increase of negative emotions, thereby allowing to clarify if patients are characterized by a general deficit in cognitive reappraisal or have specific difficulties in the down-regulation of emotions.

In **Study 2,** a new paradigm was evaluated in a sample of healthy participants. The experiment aimed to assess the effects of working memory load on the processing of concurrently presented stimuli. As outlined in a previous section, there is still some controversy regarding the effects of restricted attentional resources on the processing of emotional stimuli. On the one side, the enhancement of cognitive demands was found to attenuate the processing of emotions (e.g., Pessoa, et al., 2002; Pessoa, et al., 2005), whereas on the other side emotional stimuli were found to be processed automatically and independently of available resources (e.g., Anderson, et al., 2003; Vuilleumier, et al., 2001).

The encouraging results of attentional deployment on emotion processing resulted in **Study 3**. In this study, the effects of cognitive load on emotion processing were assessed in a sample of criminal violent offenders with BPD. The investigation of specific subpopulations, in this case offenders primarily characterized by emotional instability, might prove important for the generalizability of recent assumptions regarding delinquent behavior. Previous observations suggested that individuals with BPD are more susceptible for delinquent behavior as a result of emotional instability (Raine, 1993).

Study I: Neuronal Correlates of Cognitive Reappraisal in Borderline Patients Characterized by Emotional Instability

Chapter 2

This chapter has been published as 'Schulze, L., Domes, G., Krüger, A., Berger, C., Fleischer, M., Prehn, K., Schmahl, C., Grossmann, A., Hauenstein, K. & Herpertz, S.C. 2011. Neuronal correlates of cognitive reappraisal in borderline patients with affective instability. *Biological Psychiatry, 69, 564-73.*'

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The reader is referred to the appendix for the published article.

Study II: Effects of Cognitive Load on the Processing of Task-Irrelevant Emotional Stimuli

Chapter 3

Abstract

The present study investigated the influence of working memory load on the processing of task-irrelevant emotional stimuli. In particular, we aimed to elucidate the in(dependence) of emotional stimuli processing from the availability of cognitive resources and the role of varied emotional salience in this context. Participants (n=22) underwent functional magnetic resonance imaging (fMRI) during a working memory paradigm with low and high working memory load, and were presented with social-emotional scenes of neutral, low and high emotional salience in the background of the task. In addition, participants performed a functional localizer task, i.e. an experimental run without any background stimuli to independently determine clusters associated with enhanced working memory demands for calculation of an analysis of psychophysiological interactions (PPI). Working memory load resulted in prolonged reaction times and enhanced activation of a fronto-parietal network, including the bilateral dorsolateral prefrontal cortex and the inferior parietal gyrus. In general, higher working memory demands were accompanied by reduced activation of the bilateral amygdala and left medial-orbital prefrontal cortex. Nonetheless, highly salient stimuli elicited enhanced activity in the left amygdala under both working memory conditions compared with neutral stimuli. PPI analyses revealed a heightened negative coupling of dorsolateral structures with bilateral amygdala regions with higher working memory load. Our results suggest the extent of cognitive demands to be a crucial factor in the processing of emotional stimuli. Moreover, we suggest that the inhibitory influence on amygdala activity stems in particular from clusters of the bilateral dorsolateral prefrontal cortex.

Introduction

The individual ability to adequately cope with negative emotions is of particular interest for psychological well-being and represents an essential resilience factor for the development of psychiatric disorders (Davidson, 2000). Consequently, recent research has attempted to shed light on the underlying neural mechanisms of a wide range of emotion regulation strategies, studying inter alia the effects of anticipation (Herwig, Abler, Walter, & Erk, 2007; Nitschke, Sarinopoulos, Mackiewicz, Schaefer, & Davidson, 2006; Nitschke, et al., 2009; Wager, et al., 2004), attentional distraction (Pessoa, et al., 2002; Pessoa, et al., 2005; Vuilleumier, et al., 2001), or cognitive reappraisal (Eippert, et al., 2007; McRae, et al., 2010; Ochsner, et al., 2004). The relationship of these different forms of cognitive control of emotions can best be described along a continuum ranging from modulation of emotional responses, by means of cognitive reappraisal, to modulation of emotion perception and processing, for example by selective inattention to emotional stimuli or performance of a distracting primary task (Ochsner & Gross, 2005). Here, we studied the effects of manipulations of working memory load on the processing of simultaneously presented emotional stimuli. This represents another possibility to study the influence of attentional control on emotions, particularly as the engagement in challenging working memory tasks is known to distract people from negative emotional states and to decrease self-reported negative moods (Van Dillen & Koole, 2007).

Variants of the n-back task, asking subjects to monitor a series of consecutively presented stimuli and to press a button whenever a stimulus is the same as the one presented n-trials before, are the most popular experimental paradigm for functional studies of working memory processes, as they require on-line monitoring, updating of remembered information and response selection, thereby involving a number of key processes within working memory (Owen, McMillan, Laird, & Bullmore, 2005). Independent of the material (verbal or nonverbal) and the manipulated process (location or identity matching), studies using the n-back paradigm found consistent activation of the bilateral and medial posterior

parietal cortex, bilateral premotor cortex, dorsal cingulate cortex, bilateral rostral prefrontal cortex, bilateral dorsolateral prefrontal cortex and the bilateral mid-ventrolateral prefrontal cortex (for a meta-analysis, see Owen, et al., 2005). However, there was also evidence of enhanced activations in dorsal cingulate regions in response to nonverbal compared to verbal material, whereas verbal material resulted in enhanced activation of the left ventrolateral prefrontal cortex, bilateral medial posterior parietal cortex and thalamus.

A previous study examining the influence of a non-verbal n-back paradigm on the processing of background stimuli reported modulatory effects on perceptual processing, as working memory load reduced the increase of activity in the lateral occipital complex with enhanced image visibility (Rose, Schmid, Winzen, Sommer, & Buchel, 2005). Although emotions are known to manipulate perceptual processing in ventral stream areas (Anderson, et al., 2003; Pessoa, et al., 2002; Vuilleumier, 2005), the aforementioned effect was not yet additionally altered by emotional salience, suggesting independent influences of emotion and working memory load on perceptual processing (Glascher, et al., 2007). In contrast to previous studies demonstrating decreased amygdala activation to emotional stimuli by cognitive load (Bishop, Duncan, & Lawrence, 2004; Bishop, et al., 2007; D. G. Mitchell, et al., 2007; Pessoa, et al., 2002; Pessoa, et al., 2005), there were also no reported influences of working memory load on emotion processing in amygdala regions (Glascher, et al., 2007). However, a verbal Sternberg paradigm was found to reduce the processing of task-irrelevant emotional context with increased working memory demands, as indicated by decreased activity of the amygdala and ventral striatum (Erk, Kleczar, & Walter, 2007). Therefore, it might be assumed that the nature (verbal, non-verbal) of the working memory task represents an important factor in the diverging results of the influence on emotion processing. Further support for inhibitory influences of cognitive demands on emotional processing was generated by a recent study, which found a modulation of already full-blown emotional responses by increased task difficulty (Van Dillen, Heslenfeld, & Koole, 2009). The regulatory consequences on emotional processing are probably concerted by prefrontal areas, namely by dorsolateral, inferior and superior prefrontal cortices (e.g., Erk, et al., 2007;

Van Dillen, et al., 2009), neural structures that are consistently implicated in the cognitive reappraisal of emotions (e.g., Domes, et al., 2010; Eippert, et al., 2007; Ochsner, et al., 2002; Ochsner, et al., 2004).

In the present study, we aimed to investigate the effects of working memory load on the processing of simultaneously presented emotionally salient stimuli. Participants performed a verbal n-back task with different levels of cognitive load while viewing social scenes of varying emotional salience in the background. We expected high levels of working memory load to activate a neural network comprising prefrontal, particularly dorsolateral, and inferior parietal areas. Furthermore, we assumed that emotional background stimuli would be associated with neural responses in emotion processing areas, in particular the bilateral amygdala, and would critically depend on the availability of cognitive resources. Thus, the processing of task-irrelevant emotional stimuli was expected to be more pronounced under conditions of lower cognitive demands. Amygdala activity was assumed to directly co-vary with activation of fronto-parietal structures. In the present study, we decided to present social scenes with different levels of emotional salience, as we hypothesized that stimuli of high emotional salience might disrupt working memory processes in contrast to stimuli of low or neutral emotional salience.

Methods

Participants

Twenty-two male subjects (mean age: 28.09 ± 8.37), recruited via advertisement at the University of Rostock, were paid to participate in the study. Only male subjects were recruited in order to avoid gender influences in affective responding (Domes, et al., 2010). All participants were right-handed, had normal or corrected-to-normal visual acuity and reported no history of neurological or psychiatric disorder.

The study was approved by the institutional review board of the Medical Faculty of the University of Rostock and each subject provided written informed consent after the procedures had been fully explained.

Experimental design

All participants were scanned while performing a verbal n-back task. The task required them to monitor a series of consecutively presented letters and to press a button whenever a letter was the same as the one presented one or two trials before (1-back and 2-back level). The major focus of this study was to investigate the impact of working memory load on the processing of simultaneously presented distracting background stimuli with different levels of emotional salience. We presented high and low emotionally salient as well as neutral stimuli in the background of the task. Furthermore, participants were presented with an additional experimental run designed to assess neuronal areas generally associated with working memory demands independent of emotional salience. Hence, no distracting stimuli were presented in the background of the task.

Both runs consisted of 12 blocks each (6 blocks of 1-back and 6 blocks of 2-back) and each block lasted for 20 seconds. Prior to the start of each block, subjects viewed an instruction cue (the number 1 or 2) indicating the n-back level of the block ahead. Each block contained 10 letters with 3 targets and 7 distractors. Letters were presented for 1s in the centre of the screen followed by a blank screen of 1s. The order of the letters and the

position of the targets within a block were randomized, as was the order of all blocks within a run.

The first run was designed to be used as a functional localizer. Thus, participants viewed white letters on a grey background with no distracting pictures (n-back task without pictures) in order to assess brain areas generally associated with working memory demands. In the second run, we additionally presented distracting neutral and emotionally salient pictures in the background of the letters (n-back task with pictures). Participants were instructed to ignore the stimuli and to focus exclusively on the working memory task. We selected 40 neutral pictures (arousal: 1.71 ± 0.34; valence: 5.51 ± 0.32; 9-point rating scale), 40 negative pictures with low emotional salience (arousal: 4.65 ± 0.54; valence: 3.55 ± 0.30), and 40 negative pictures with high emotional salience (arousal: 6.49 ± 0.50; valence: 1.96 ± 0.38) from the International Affective Picture system (IAPS, Lang, Bradley, & Cuthbert, 2008) and another similar set composed in our laboratory. Each block contained stimuli of only one salience level (neutral, low or high emotionally salient stimuli, respectively). Consequently, we were able to independently vary the factors “working memory load” (1-back and 2-back) and “emotional salience” (neutral, low and high salience) in a 2x3 factorial design.

After the experiment, participants were presented with a surprise recognition task. The task consisted of 72 trials including 36 pictures that were previously shown in the experiment and 36 new pictures. Participants were asked whether they had seen the picture before on a 4-point rating scale (unknown, sure; unknown, unsure; known, unsure; known, sure). The 36 new pictures did not differ in their emotional salience from the previously presented pictures. Recognition data were not available for two participants due to technical reasons.

Prior to the experiment, all subjects completed a training session on the n-back task both with and without pictures to ensure appropriate understanding of the task ahead. In the training session, we used different pictures than in the experiment.

Magnetic resonance imaging

We acquired whole brain imaging data using a 1.5 T scanner (Magnetom Avanto, Siemens, Erlangen, Germany) equipped with a standard head coil. Head movement was minimized using foam cushions. Visual stimulation was presented via a pair of stereoscopic MRI-compliant goggles (VisuaStim, Resonance Technology, Los Angeles, USA). Axially oriented functional images (T2*-weighted volumes) were obtained using standard parameters (TE = 40ms; TR = 2700ms; flip angle: 90°; FOV = 192mm; matrix = 64 x 64; voxel size = 3x3x3mm³, 36 slices). Data were recorded in 2 runs, each consisting of 130 volumes. After acquisition of functional images, a sagittally oriented T1-weighted structural scan was acquired (TE = 3.9ms; TR = 1500ms; flip angle: 15°; matrix = 256 x 256; voxel size = 1x1x1mm³, 160 slices).

Behavioral data analysis

Statistical analyses were performed using SPSS 17 (SPSS Inc., Chicago, IL, USA). The significance level for all tests was $p<.05$. Reaction times (RT) and errors were analyzed using repeated-measures ANOVAs. Greenhouse-Geisser corrections were applied if the assumption of sphericity was violated. The retrieval scores were binarized not factoring the safety ratings into subsequent calculations of hits and false alarm rates. In addition, discrimination indices ($d' = Z_{hits} - Z_{false\ alarms}$) were calculated for each subject and condition, following a classical signal detection theory approach (Macmillan & Creelman, 1991).

Image analysis

MRI data analysis was conducted using the Statistical Parametric Mapping software (SPM5, Wellcome Department of Imaging Neuroscience, London, UK) implemented in MATLAB 7.0.4 (Mathworks Inc., Sherborn, MA, USA).

The two runs (n-back task without and with distracting background pictures) were analyzed separately. The first four scans of each run were discarded due to T1 equilibration effects. The remaining functional images were slice-time corrected, realigned and unwarped,

co-registered to the individual anatomical images, spatially normalized to the Montreal Neurological Institute (MNI) space and smoothed using a 8mm full-width at half-maximum Gaussian kernel. After pre-processing, changes in the blood oxygen level-dependent (BOLD) signal were calculated at the single subject level. We included regressors for each condition, which were modeled using a convolution of the hemodynamic response function (HRF) with boxcar functions of 20 seconds for the respective six conditions. The main effects of each condition were entered into group analyses.

At the group level, we employed a paired t-test for the *n-back* task without pictures and a random effects flexible factorial design for the *n-back* task with pictures (subject x n-back x picture salience). Clusters for main effects of the experiment (emotional salience and working memory load) were corrected for family-wise errors (with an additional extent threshold of at least 5 voxels). For whole-brain main effects and interactions of working memory load by emotional salience, we report clusters of voxels that survived statistical thresholding at $p < .001$ (uncorrected) and had a cluster size of at least 21 voxels resulting in a corrected $p < 0.05$ as determined using Monte Carlo simulation implemented in AFNI's (Analysis of Functional NeuroImages; www.afni.nimh.nih.gov, Cox, 1996) AlphaSim. Coordinates of significant activations are reported in MNI space. Regions-of-interest analyses and small volume corrections were conducted in the amygdala as defined by the Automated Anatomical Labeling software (AAL, Tzourio-Mazoyer, et al., 2002). The extraction and calculation of the percent signal change was conducted with RFXPlot (Glascher, 2009).

Finally, we carried out PPI analyses to capture functional interactions of brain regions related to the experimental design (Friston, et al., 1997). In particular, we were interested in the fronto-parietal network associated with working memory load and its influence on the bilateral amygdala. We used seed regions unbiased from emotional salience by analyzing the *n-back task without pictures* (functional localizer task). We calculated the results of the contrast assessing working memory load (2-back > 1-back) and determined the peak voxel of the whole group in the bilateral dorsolateral prefrontal cortex (left:[-30,3,60]; right: [27,6,63])

as well as the bilateral inferior parietal gyrus (left:[-27,-51,39]; right: [36,-54,39]). Subsequently, we extracted the individual time course of activity from the *n-back task with pictures* using a sphere of 6mm and calculated the mean time series to account for both hemispheres in one model. These time courses were de-convolved to remove the effect of the HRF, multiplied by the psychological regressors of interest and re-convolved with the canonical HRF. The resulting contrast images for each subject were entered into a 2^{nd}-level random effects analysis using one-sample t-tests, thereby identifying brain areas showing a significant co-variation with the activity of the bilateral dorsolateral prefrontal cortex or inferior parietal gyrus during enhanced working memory load. Clusters of whole-brain analysis are reported if they survived statistical thresholding at $p<.001$ (uncorrected) and had a cluster size of at least 21 voxels, again resulting in a corrected $p< 0.05$ as determined by Monte Carlo simulations. Small volume corrections were additionally conducted in the bilateral amygdala.

Results

Behavioral data

Behavioral analysis showed a main effect of working memory load, as participants had prolonged reaction times ($F(1,21) = 15.39$, $p<.01$) and a higher rate of missed targets ($F(1,21) = 17.90$, $p<.001$) under conditions of higher working memory load. However, participants' reaction times (RT) or hit rates were not influenced by emotional salience of background stimuli, as the analysis showed neither a main effect of emotional salience (RT: $F(2,42) = 0.56$, $p>.50$; Hit rate: $F(2,42) = .52$, $p>.50$) nor an interaction between emotional salience and working memory level (RT: $F(2,42) = 1.33$, $p>.20$; Hit rate: $F(2,42) = .11$, $p>.90$). False alarm rates were not influenced by salience of the background stimuli, but we found a higher rate of false alarms in blocks with enhanced working memory demands ($F(1,21) = 4.34$, $p<.05$). Descriptive data are presented in Table 3.1.

Table 3.1.

Response Latencies During the n-Back Task with Background Stimuli. .

a. Response Latencies

	Reaction times (in ms)		*Hit Rates (in %)*	
	M	*SD*	*M*	*SD*
1-back	524	74	95.96	10.02
neutral	523	80	96.97	08.35
low	516	90	96.97	14.21
high	531	92	93.94	13.16
2-back	588	83	87.12	14.89
neutral	597	95	87.12	18.50
low	606	148	87.88	17.95
high	562	91	86.36	19.68

To further explore the consequences of working memory load on the processing of background stimuli, we analyzed retrieval scores of the surprise recognition task. Participants showed a bias to more strongly affirm the previous presentation of emotionally salient stimuli, as revealed by an analysis of false alarm rates ($F(1.54,38) = 13.64$, $p<.001$). As a consequence, we calculated d' and took the individual response bias into account (see Table 3.2). Statistical analyses showed that participants had difficulties to remember stimuli shown in blocks with high working memory load ($F(1,19) = 22.24$, $p<.001$) and, furthermore, had a tendency to retrieve emotionally salient stimuli better ($F(1.41,38) = 3.64$, $p<.10$). Post-hoc *t-tests* showed that participants were significantly better able to retrieve highly salient stimuli compared to neutral ($t(19) = 2.09$, $p<.05$) and low salient stimuli ($t(19) = 2.28$, $p<.05$). There was no interaction of picture category and working memory level ($F(2,38) = .264$, $p>.70$).

Table 3.2.

Retrieval scores of the Presented Stimuli.

b. Retrieval scores

	Hit Rates (in %)		*False Alarm Rate (in %)*		*d'*	
	M	*SD*	*M*	*SD*	*M*	*SD*
Neutral	35.00	21.39	16.67	19.31	1.24	1.01
1-back	28.33	35.91			1.57	1.16
2-back	41.67	31.76			0.92	1.18
Low	57.92	19.77	22.08	18.99	1.49	1.33
1-back	69.17	21.13			1.92	1.22
2-back	46.67	24.54			1.05	1.21
High	67.08	18.03	41.25	17.41	1.90	1.33
1-back	75.00	20.59			2.26	1.51
2-back	59.17	23.24			1.55	1.31

Effects of emotional salience and working memory load on amygdala activity

We began by conducting regions-of-interest analyses of the amygdala. In line with our hypotheses, we found a main effect of working memory load in the bilateral amygdala (left amygdala: $F(1,21) = 19.43$, $p<.001$; right amygdala: $F(1,21) = 10.43$, $p<.01$) driven by decreased amygdala activity during blocks with high working memory load (see Figure 3.1). In addition, there was also a significant effect of emotional saliency in the left amygdala ($F(2,42) = 4.70$, $p<.05$), reflecting enhanced processing of highly salient compared to neutral stimuli ($t(21) = 3.79$, $p<.01$ [Bonferroni adjusted]). Statistical analyses revealed no interaction between emotional salience and working memory load either in the left ($F(2,42) = .88$, $p>.40$) or in the right amygdala ($F(2,42) = .39$, $p>.60$).

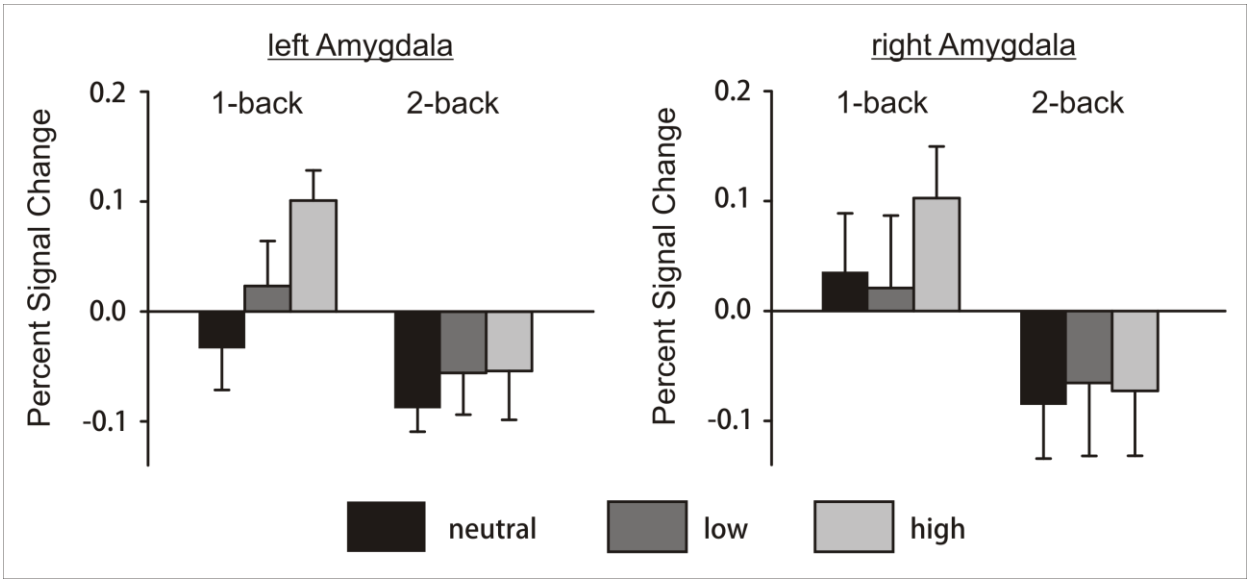

Figure 3.1. **Regions-of-interest analyses of the bilateral amygdala.** Statistical analyses of BOLD activity suggest a working memory load-dependent activation of the bilateral amygdala. In the left amygdala, we also found a main effect of emotion ($F(2,42) = 4.70$, $p=.014$). Figures depict the mean percent signal change +/- standard error of mean.

Whole brain analysis

Main effects of working memory load

Independent of emotional salience, we found enhanced working memory load to be associated with activation of a fronto-parietal network (see Figure 3.2a and Table 3.3a) involving the bilateral dorsolateral prefrontal cortex, inferior parietal gyrus, precuneus and supplementary motor area.

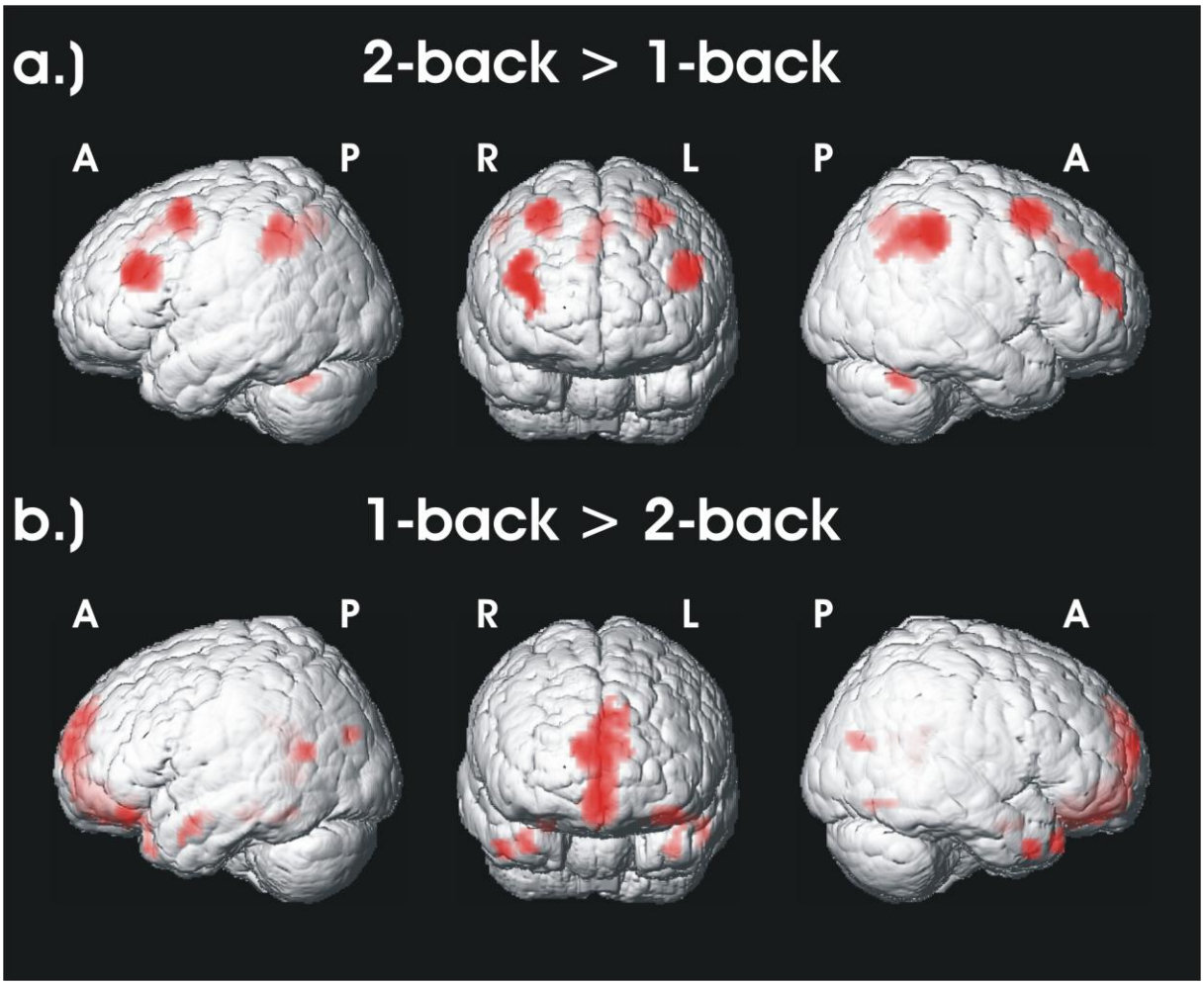

Figure 3.2. **Neural correlates of working memory load.** Cluster with p<.05 (FWE-corrected) and an extent threshold of at least 10 voxels.

Table 3.3.

Significant Clusters of Neural Activation Associated with the Effects of Working Memory Load Independent of Emotionally Salient Background Stimuli. Cluster with p<.05 (FWE Corrected) and Extent Threshold of at Least 10 Voxels.

Region		Coordinates x	y	z	k	Z
a. 2-back > 1-back						
Superior frontal g., dorsolateral	L	-30	3	60	112	7.37
Inferior parietal g.	R	42	-42	45	282	6.95
Inferior parietal g.	R	54	-42	51	LM	6.32
Inferior parietal g.	R	48	-51	51	LM	6.11
Inferior frontal g., triangular	L	-48	27	30	133	6.83
Superior frontal g., dorsolateral	R	30	3	60	163	6.81
Middle frontal g.	R	39	45	21	148	6.81
Superior frontal g., dorsolateral	R	36	57	9	LM	4.87
Inferior parietal g.	L	-42	-45	51	144	6.72
Inferior parietal g.	L	-39	-45	42	LM	6.49
Precuneus	R	6	-63	54	139	6.60
Precuneus	L	-9	-63	54	LM	6.06
Cerebellum	R	30	-63	-27	51	6.29
Cerebellum	R	39	-57	-30	LM	5.64
Cerebellum	L	-30	-63	-30	25	6.04
Supplementary motor area	L	-6	9	54	74	5.96
Supplementary motor area	R	3	18	51	LM	5.70
Supplementary motor area	R	3	24	45	LM	5.47
b. 1-back > 2-back						
Superior frontal g., medial-orbital	L	-3	60	18	598	>8
Superior frontal g., medial-orbital	L	-3	48	-6	LM	7.57
Superior frontal g., medial-orbital	L	-3	60	-3	LM	7.38
Posterior cingulate g.	L	-6	-51	27	392	7.64
Posterior cingulate g.	R	3	-54	24	LM	6.89
Posterior cingulate g.	L	-6	-51	9	LM	6.52
Temporal pole	R	36	24	-30	16	6.35
Inferior frontal g., orbital	L	-33	30	-15	50	6.03
Temporal pole	L	-39	21	-30	LM	5.30
Temporal pole	L	-42	24	-18	LM	5.06
Medial occipital g.	L	-27	-87	27	20	5.87
Temporal pole	R	48	9	-33	19	5.78
Amygdala/Hippocampus	L	-21	-9	-15	11	5.73
Middle temporal g.	L	-57	-3	-21	25	5.62
Middle temporal g.	L	-48	-60	18	34	5.61
Parahippocampal g.	L	-24	-36	-12	20	5.55
Fusiform g.	L	-27	-54	-15	17	5.50
Middle occipital g.	R	33	-78	21	28	5.43
Superior occipital g.	R	30	-84	27	LM	5.28
Amygdala/Hippocampus	R	24	-6	-21	10	5.38
Amygdala	R	30	3	-18	LM	4.90

Note. * - Small Volume Correction, g – gyrus, k – Cluster size in voxel, L - left hemisphere, LM - local maximum, R - right hemisphere

The reverse contrast displayed significant activation of clusters in both temporal poles, bilateral occipital areas and the bilateral precuneus (see Figure 3.2b and Table 3.3b). Additionally, we found significant clusters in the left medial-orbital prefrontal cortex and left posterior cingulate cortex. Importantly, the whole-brain analysis supported the findings of the regions-of-interest analyses in the amygdala, as we found enhanced activation of clusters in the bilateral amygdala-hippocampal region during blocks with lower working memory demands.

Main effect of emotional salience

Subsequently, we analyzed neural correlates of picture salience independent of working memory load. The processing of highly salient compared to neutral stimuli in the background of the task significantly activated clusters in the medial prefrontal cortex, the right inferior frontal gyrus, as well as the bilateral middle temporal and right inferior occipital gyrus. There was also increased activation of the left amygdala ([-24,6,-18]: Z=4.14, k=20, p=.001 [small volume corrected]) to highly salient compared with neutral stimuli. In addition, contrasting high with low salient stimuli revealed enhanced activation of the right inferior temporal gyrus and the left amygdala ([-21,-3,-18]: Z=3.05, k=6, p=.035 [small volume corrected]).

Interactions of working memory load and emotional salience

First, and in accordance with our hypotheses, we investigated the impact of working memory load within each picture category. The respective analyses (i.e. 1-back^{high} > 2-back^{high}) revealed enhanced activity of the bilateral amygdala during low working memory demands if highly salient stimuli (left amygdala: [-21,-6,-12], Z=4.43, k=15, p<.001 [small volume corrected]; right amygdala: [24,-3,-21], Z=3.56, k=28, p=.007 [small volume corrected]) or low salient stimuli were presented in the background of the working memory task (left amygdala: [-24,-9,-15], Z=3.24, k=8, p =.021 [small volume corrected]; right amygdala: [27,0,-18], Z=3.94, k=26, p=.002 [small volume corrected]). Moreover, this pattern was also evident during the presentation of neutral stimuli in the background of the task (left amygdala: [-24,-

9,-15], Z=3.87, k=3, =.003 [small volume corrected]; right amygdala: [24,-9,-15], Z=3.62, k=20, p=.006 [small volume corrected]), thereby suggesting a general decrease in amygdala activity with enhanced working memory demands. Importantly, additional analyses (i.e. $High^{1\text{-}back>2back}$ > $Low^{1\text{-}back>2\text{-}back}$) revealed no differences in the extent of decrease in amygdala activity between salience categories.

Additional interactions were calculated to assess salience-dependent activation of the neural network associated with working memory load and hence restricted to fronto-parietal clusters by applying an inclusive mask of the main effect of load. A small cluster in the left inferior frontal gyrus showed enhanced activation during the presentation of low salient compared to highly salient stimuli ($Low^{2back>1back}$ > $High^{2back>1back}$). There were no further differences in the neural correlates of working memory load between salience levels and there were also no differences between blocks with negative and neutral background stimuli.

Finally, we thoroughly calculated single comparisons between salience categories for each level of working memory load. We started by calculating neural differences during low-level working memory load (see Table 3.4). The presentation of highly salient compared to neutral stimuli was associated with enhanced activation of bilateral inferior temporal and occipital gyrus, as well as parts of the orbitofrontal and superior frontal cortex. Furthermore, we found the left amygdala to show significantly enhanced activation. The reverse contrast showed stronger activation of a cluster in the right parahippocampal gyrus.

Table 3.4.

Significant Clusters of Neural Activation Contrasting Emotional Salience Categories During Low Working Memory Load. Cluster with p<.001 (uncorr.) and Extent Threshold of at least 21 Voxels.

Region		Coordinates x	y	z	k	Z
a. $High^{1\text{-}back}$ > $Neutral^{1\text{-}back}$						
Inferior temporal g.	R	45	-66	-9	690	5.89
Inferior temporal g.	R	54	-66	-6	LM	5.74
Inferior occipital g.	R	42	-78	-9	LM	5.62
Middle temporal g.	L	-54	-63	3	572	5.42
Inferior temporal g.	L	-48	-66	-9	LM	5.09
Inferior occipital g.	L	-51	-75	-6	LM	4.79
Inferior frontal g., triangular	R	51	39	9	53	5.11

Table 3.4 (continued)

Region		Coordinates x	y	z	k	Z
a. High$^{1\text{-back}}$ > Neutral$^{1\text{-back}}$						
Inferior frontal g., orbital	L	-39	24	-21	123	4.76
Inferior frontal g., triangular	L	-48	21	0	LM	3.71
Superior occipital g.	R	24	-63	42	40	3.60
Fusiform g.	L	-33	-42	-24	41	4.36
No ROI	R	15	-30	-30	25	4.32
No ROI	R	21	-24	-39	LM	3.49
Superior frontal g., medial	R	3	63	24	94	4.14
Superior frontal g., medial	L	-3	48	39	LM	3.96
Precentral g.	R	45	6	30	28	4.04
Precentral g.	R	42	6	42	LM	3.47
Cerebellum	L	-21	-72	-45	22	3.96
Precuneus	L	-15	-63	66	26	3.63
Superior parietal g.	L	-21	-66	60	LM	3.38
Superior parietal g.	L	-21	-57	51	LM	3.31
Amygdala*	L	-24	-3	-15	29	2.95
b. Neutral$^{1\text{-back}}$ > High$^{1\text{-back}}$						
Parahippocampal g.	R	27	-45	-3	57	4.41
c. High$^{1\text{-back}}$ > Low$^{1\text{-back}}$						
Inferior temporal g.	R	48	-66	-9	323	5.63
Inferior occipital g.	R	36	-78	-12	LM	4.14
c. High$^{1\text{-back}}$ > Low$^{1\text{-back}}$						
Fusiform g.	R	42	-45	-15	LM	4.12
Inferior frontal g., opercular	R	42	12	33	49	4.56
Inferior temporal g.	L	-45	-60	-6	210	4.28
Middle temporal g.	L	-63	-60	0	LM	4.11
Middle temporal g.	L	-51	-60	3	LM	4.05
Inferior frontal g., triangular	R	45	33	6	26	4.21
Supplementary motor area	L	-6	18	45	38	4.13
Superior frontal g., medial	L	-9	30	42	LM	3.98
Superior frontal g., dorsolateral	L	-15	39	42	LM	3.66
Cerebellum	L	-18	-66	-42	27	4.12
Cerebellum	L	-27	-69	-48	LM	3.41
Cerebellum		0	-45	0	27	3.93
Cerebellum	L	-33	-60	-27	28	3.78
Fusiform g.	L	-36	-45	-21	LM	3.70
Inferior frontal g., orbital	L	-39	18	-6	21	3.52
d. Low$^{1\text{-back}}$ > High$^{1\text{-back}}$						
No suprathreshold clusters						
e. Low$^{1\text{-back}}$ > Neutral$^{1\text{-back}}$						
Temporal pole	L	-36	21	-24	28	3.91
Superior frontal g., medial		0	63	24	21	3.86
f. Neutral$^{1\text{-back}}$ > Low$^{1\text{-back}}$						
No suprathreshold clusters						

Note. * - Small Volume Correction, g – gyrus, k – Cluster size in voxel, L - left hemisphere, LM - local maximum, R - right hemisphere

Contrasting high with low salient stimuli instead revealed significant clusters in the bilateral temporal gyrus, bilateral inferior frontal and left superior frontal cortex, whereas there were no significant clusters in the reverse contrast. Finally, we found the background presentation of low salient stimuli to significantly activate clusters in the left temporal pole and bilateral medial prefrontal cortex.

Single comparisons during high working memory load revealed enhanced activation of the left amygdala if highly salient compared to neutral stimuli were presented in the background of the task ($High^{2\text{-back}}$ > $Neutral^{2\text{-back}}$). Additional clusters were found in the bilateral medial and right medial-orbital prefrontal cortex, as well as parts of the right middle and inferior temporal gyrus and occipital structures. The reverse contrast displayed stronger activation of the left cuneus and calcarine fissure (see Table 3.5).

Table 3.5.

Significant Clusters of Neural Activation Contrasting Emotional Salience Categories During High Working Memory Load. Cluster with p<.001 (uncorr.) and Extent Threshold of at least 21 Voxels.

Region		Coordinates x	y	z	k	Z
a. $High^{2\text{-back}}$ > $Neutral^{2\text{-back}}$						
Middle temporal g.	R	54	-66	0	132	4.72
Inferior temporal g.	R	48	-69	-6	LM	4.65
Inferior occipital g.	R	39	-75	-12	LM	3.93
Superior frontal g., medial	L	-6	60	30	58	4.11
Superior frontal g., medial		0	54	18	LM	3.76
Superior frontal g., medial	R	12	51	15	LM	3.29
Superior frontal g., medial-orbital	R	6	51	-9	21	3.90
Middle occipital g.	L	-48	-84	9	21	3.75
Middle occipital g.	L	-51	-78	15	LM	3.74
Amygdala*	L	-24	6	-18	8	3.35
b. $Neutral^{2\text{-back}}$ > $High^{2\text{-back}}$						
Cuneus	L	-3	-87	18	29	3.94
Calcarine fissure	L	-9	-78	15	LM	3.51
c. $High^{2\text{-back}}$ > $Low^{2\text{-back}}$						
Superior frontal g., orbital	L	-33	33	-18	22	4.30
Middle occipital g.	L	-36	-84	24	24	3.90
d. $Low^{2\text{-back}}$ > $High^{2\text{-back}}$						

No suprathreshold clusters

Table 3.5 (continued)

Region		Coordinates x	y	z	k	Z
e. Low$^{2\text{-back}}$ > Neutral$^{2\text{-back}}$						
No suprathreshold clusters						
f. Neutral$^{2\text{-back}}$ > Low$^{2\text{-back}}$						
Parahippocampal g.	R	30	-42	-6	27	4.01

Note. * - Small Volume Correction, g – gyrus, k – Cluster size in voxel, L - left hemisphere, LM - local maximum, R - right hemisphere

Furthermore, there was enhanced activation in the left orbitofrontal cortex and left middle occipital gyrus when comparing high with low salient stimuli, whereas the reverse contrast displayed no significant clusters. We found no enhanced activation of clusters contrasting low salient with neutral stimuli, whereas the reverse contrast (Neutral$^{2\text{-back}}$ > Low$^{2\text{-back}}$) found a stronger activation of the right parahippocampal gyrus.

Psychophysiological interactions

As mentioned earlier, we were particularly interested in the impact of enhanced working memory load on neural activity in the amygdala. Therefore, we conducted PPI analyses to investigate the functional coupling between the fronto-parietal network, namely of clusters of the bilateral dorsolateral prefrontal cortex and bilateral inferior parietal cortex, which were independently determined, and the amygdala. Since the fMRI results implied a general decrease of neural activity in the amygdala during conditions with higher working memory load, we calculated PPI analyses independent of salience of the background stimuli. Thus, here, we aimed to assess changes in functional coupling related to working memory load (2-back > 1-back).

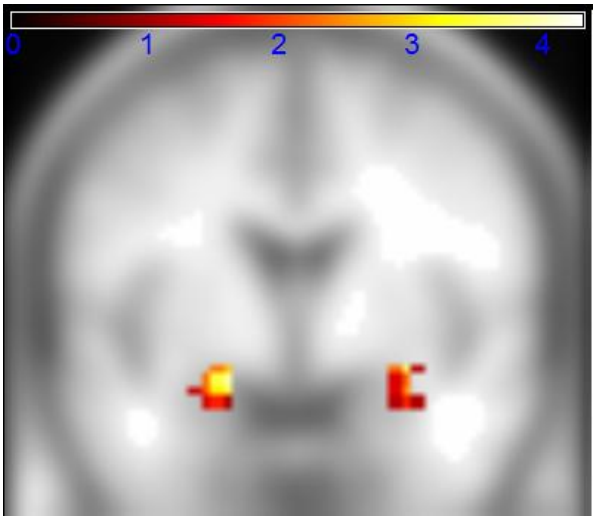

Figure 3.3. **Functional coupling of the amygdala and dorsolateral prefrontal cortex as a result of working memory load**. T-values are overlaid on participants' structural mean image smoothed with a Gaussian kernel of 6mm

Activity in the bilateral dorsolateral prefrontal cortex was positively coupled with a huge cluster comprising the left middle occipital gyrus, the left lingual gyrus and the left calcarine fissure. Furthermore, there were negative associations with neural activity of parts of the right precuneus, the left median cingulate gyrus and left medial prefrontal cortex. Most importantly, we also found negative associations with the left amygdala (left amygdala: [-21,-6,-15]: Z=3.58, k=8, p=.010 [small volume corrected]; and right amygdala: [30,0,-18]: Z=2.88, k=4 p=.062 [small volume corrected]), suggesting increased activity of the dorsolateral prefrontal cortex to reduce amygdala activity independent of salience level (see Figure 3.3).

Additional analyses demonstrated an enhanced negative coupling of the dorsolateral prefrontal cortex and the right amygdala ([24,0,15]: Z=4.02, p=.002 [small volume corrected]) during the presentation of salient compared to neutral stimuli under enhanced working memory conditions. The co-variation of amygdala and dorsolateral prefrontal activity did not differ between low and highly salient stimuli.

Table 3.6.

Clusters Exhibiting Significant Psychophysiological Interactions with the Bilateral Dorsolateral Prefrontal Cortex or Inferior Parietal Gyrus with Higher Working Memory Load, but Independent of Salience Category. Cluster with p<.001 (uncorrected) and Extent Threshold of 21 Voxels.

Region		Coordinates x	y	z	k	Z
a. Positive Coupling with Dorsolateral Prefrontal Cortex						
Middle occipital g.	L	-33	-84	12	1313	5.12
Lingual g.	L	-9	-84	-15	LM	4.70
Calcarine fissure	L	-3	-93	9	LM	4.69
b. Negative Coupling with Dorsolateral Prefrontal Cortex						
Cerebellum	L	-30	-78	-33	58	4.68
Cerebellum	L	-21	-75	-33	LM	3.49
Precuneus	R	6	-51	24	60	4.48
Precuneus		0	-66	18	LM	3.63
Calcarine fissure	R	9	-51	33	LM	3.13
Precuneus	R	21	-57	24	25	4.43
Median cingulate g.	L	-9	-33	42	107	4.42
Median cingulate g.	L	-6	-24	42	LM	4.20
Median cingulate g.		0	-21	36	LM	4.19
Medial prefrontal cortex	L	-12	60	15	25	4.10
Amygdala*	L	-21	-6	-15	8	3.58
c. Positive Coupling with Inferior Parietal Gyrus						
Middle occipital g.	L	-36	-84	9	48	4.32
Cuneus	R	12	-93	18	55	4.28
Superior occipital g.	R	24	-93	15	LM	3.47
Precentral g.	L	-48	6	39	62	4.01
Inferior frontal g. – triangular	L	-45	15	24	LM	3.81
Inferior frontal g. – triangular	L	-51	18	18	LM	3.30
Calcarine fissure	R	6	-78	3	30	3.86
Lingual g.	L	-27	-57	-9	22	3.58
Fusiform g.	R	27	-69	-15	24	3.49
d. Negative Coupling with Inferior Parietal Gyrus						
Angular g.	R	48	-69	45	23	4.65
Medial prefrontal cortex	R	18	42	24	26	4.42
Medial prefrontal cortex	R	12	45	30	LM	3.22
Median cingulate g.		0	-21	36	24	4.13
Precuneus	R	6	-72	39	22	4.01
Precuneus	R	15	-57	30	27	3.96
Posterior cingulate g.	R	9	-48	30	LM	3.62

Note. * - Small Volume Correction, g – gyrus, k – Cluster size in voxel, L - left hemisphere, LM - local maximum, R - right hemisphere

Increased activity in the bilateral inferior parietal gyrus was positively coupled with the left middle and superior occipital gyrus, the left precentral and inferior frontal gyrus, the left lingual gyrus as well as the right calcarine fissure and fusiform gyrus. The activity was negatively coupled with the right angular gyrus and middle prefrontal cortex, and the right precuneus and posterior cingulate gyrus. We found no coupling of the inferior parietal gyrus with parts of the amygdala.

Discussion

In the present study, we investigated the interference of task-irrelevant emotionally salient stimuli with different levels of working memory load. Activation in the fronto-parietal network, comprising clusters in the bilateral dorsolateral prefrontal cortex and inferior parietal gyrus, was associated with increased cognitive load during the working memory task. Moreover, higher cognitive load was accompanied by reduced activity in the bilateral amygdala, pointing to an inhibitory influence of cognitive load on the processing of task-irrelevant emotionally salient stimuli. In turn, lower cognitive load was associated with enhanced activations in the left medial-orbital prefrontal and posterior cingulate cortex as well as the bilateral amygdala-hippocampal complex, regions that are commonly involved in the evaluation of emotional stimuli and emotional arousal (e.g., Phan, et al., 2004). In addition, we found enhanced activity of the amygdala when emotionally salient stimuli were presented in the background of the working memory task. Interestingly, enhanced processing of highly salient compared to neutral stimuli was not only evident under conditions of low working memory, but also under conditions of high working memory load. Thus, prioritized processing of highly salient stimuli is still present under conditions of high cognitive load. Taken together, our results suggest that cognitive load, associated with the working memory task, interferes with the processing of task-irrelevant emotionally salient stimuli.

The finding that neural activity in the bilateral amygdala is reduced with higher cognitive load is in line with previous studies showing that the processing of task-irrelevant emotional stimuli depends on the availability of cognitive resources (e.g., D. G. Mitchell, et al., 2007; Pessoa, et al., 2002; Pessoa, et al., 2005). Tasks with high cognitive demands were found to significantly reduce activity of regions implicated in emotion processing. Our results concur with these findings, as we demonstrate a general reduction of activity in the amygdala as well as of dorso- and ventromedial parts of the prefrontal cortex with enhanced cognitive load. The reduced activity in medial prefrontal structures by cognitive load might be explained by a disruption of conscious evaluation of task-irrelevant background stimuli.

Medial prefrontal structures are consistently implicated in emotional responding, more particularly in the appraisal of stimuli (Kalisch, Wiech, Critchley, & Dolan, 2006; Ochsner, et al., 2009), self-referential processing (D'Argembeau, et al., 2007; J. P. Mitchell, Banaji, & Macrae, 2005) and social cognition (for a discussion, see Amodio & Frith, 2006). The disruption of conscious evaluation might be a result of modulations in gaze and fixation patterns. Subjects might show load-dependent exploration behavior of concurrently presented background stimuli and low cognitive demands might be accompanied by more extensive visual scanning of stimuli as compared to conditions of higher cognitive demands. Consequently, future studies should investigate the modulatory effects of eye movements on neural activity, as cognitive load might inhibit overt attention for emotional stimuli and might thereby reduce activation of limbic structures. Accordingly, a recent study found that gaze fixations predicted neural activity in emotion processing areas during the voluntarily regulation of picture-induced negative affect (van Reekum, et al., 2007). However, in the present study, gaze fixation might have played a subordinate role. Recently, van Dillen et al. (2009) prevented the possible influence of alterations in visual exploration of task-irrelevant stimuli, as participants performed a challenging working memory task after viewing emotional stimuli. They also found that cognitive load modulated neural activity emotion processing areas.

Most importantly, the present results directly trace the inhibitory influence of cognitive load on emotion processing to dorsolateral structures of the prefrontal cortex. In the present study, participants performed a functional localizer task, i.e. an additional run without background stimuli, thereby allowing an independent determination of coordinates within the dorsolateral prefrontal cortex and the inferior parietal gyrus for subsequent analysis of functional connectivity. These clusters were exclusively associated with working memory load and subsequently used as seed regions in analyses of psychophysiological interactions. The respective results revealed a heightened negative coupling of the bilateral dorsolateral prefrontal cortex, but not the inferior parietal gyrus, with the amygdala. Although psychophysiological interactions do not allow causal interpretations in a strict sense, the

independent determination of the seed region based on independent data, together with previous findings implicating the dorsolateral prefrontal cortex in the regulation of emotions (e.g., Eippert, et al., 2007; Erk, et al., 2007; Herwig, Baumgartner, et al., 2007; Leyman, De Raedt, Vanderhasselt, & Baeken, 2009; Van Dillen, et al., 2009), strongly suggest that the activity in the dorsolateral PFC (and its stronger activation with enhanced cognitive load) inhibited amygdala activity in the present study. Supporting evidence for this interpretation was gathered by Leyman and colleagues (2009), who used high-frequency repetitive transcranial magnetic stimulation to disrupt functioning of the dorsolateral PFC, which resulted in pronounced deficits to inhibit the processing of negative information.

Current theoretical frameworks of emotion regulation argue for different stages on a time continuum at which regulatory actions can take place: the modulation of emotion perception at early stages and the modulation of emotional appraisal and emotional responses at later stages (for a discussion, see Ochsner, et al., 2002; Ochsner & Gross, 2005). A study investigating two common response-focused strategies in the regulation of emotions, namely reappraisal of aversive stimuli versus suppression of emotional responses, found significant differences in BOLD activity of limbic structures and the temporal dynamics of PFC responses (Goldin, McRae, Ramel, & Gross, 2008). In addition, previous research also demonstrated extensive differences in short- and long-term effects on affect, memory and social relations (for a review, see John & Gross, 2004). In the present study, we show that the engagement in a cognitively demanding task represents one way to modulate the processing of emotional stimuli and consequently early stages along theoretical frameworks of emotion regulation. This is supported by neural and also behavioral data, as we found impaired memory performance for concurrently presented background stimuli. Additional research is needed to better characterize the consequences of cognitive distraction from emotion processing, especially for psychological health and well-being, and directly evaluate antecedent- and response-focused strategies of emotion regulation. A recent study compared the neural mechanisms associated with cognitive distraction and reappraisal and found different consequences for emotional experiences. Cognitive distraction led to greater

decreases in amygdala activity and enhanced activation of prefrontal-parietal regions, whereas cognitive reappraisal was reported to result in enhanced activation of medial prefrontal cortices associated with evaluation of affective meaning and self-referential processing (McRae, et al., 2010).

The investigation of cognitive load and attentional distraction on emotion processing is of particular interest in patients characterized by difficulties in emotion regulation. For instance, deficits in emotion regulation abilities are considered a hallmark of borderline personality disorder psychopathology (Linehan, 1995). Borderline patients show enhanced negative affect to aversive stimuli (Herpertz, Dietrich, et al., 2001; Minzenberg, et al., 2007) and have pronounced deficits using emotion regulation strategies, such as distancing (Koenigsberg, Fan, et al., 2009), which possibly leads to the use of self-injurious behavior for the regulation of negative emotions (Niedtfeld, et al., 2010). However, less is known whether these difficulties are exclusively restricted to full-blown emotional responses. Thus, additional research in this domain might help to characterize patients' difficulties along the continuum of emotion regulation as proposed by Ochsner and Gross (2005). Distraction techniques are partly taught in cognitive behavioural therapy. The presented results support the engagement in cognitively demanding tasks as a useful approach for the immediate regulation of negative affect and might be of particular interest for a more widespread therapeutic imparting.

Taken together, the present study shows that increased cognitive load in the context of a working memory task recruits a fronto-parietal network, mainly of clusters in the bilateral dorsolateral prefrontal cortex and the inferior parietal gyrus, and exerts an inhibitory influence on amygdala activity. Moreover, we provide evidence that the amygdala is inhibited by the dorsolateral prefrontal cortex, which shows a heightened negative coupling with the amygdala during increased working memory demands.

Study III: Effects of Emotional Stimuli on Working Memory Processes in Male Criminal Offenders with Borderline and Antisocial Personality Disorder

Chapter 4

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The reader is referred to the appendix for the published article.

General Discussion

Chapter 5

Emotional instability is consistently proposed to be the most characteristic feature of patients with BPD and was previously shown to be directly related to many aspects of BPD psychopathology. In particular, altered processing and regulation of emotions are assumed to underlie the difficulties that patients experience in their everyday life.

The studies presented in the previous chapters investigated the neurobiological correlates of two distinct emotion regulation strategies, i.e., attentional deployment and cognitive reappraisal. The implications of the presented findings for the understanding of the neurofunctional basis of BPD and theoretical conceptualizations of emotional instability will be discussed in the following sections.

The final part of this chapter will provide a discussion of study limitations and an outlook on future research directions.

Neurofunctional Alterations in BPD

The implications of the neurofunctional findings presented in the previous chapters will be addressed in the following section. Further implications for the theoretical understanding of emotional instability in BPD will be addressed in a later section. Thus, here I will focus on alterations of limbic and paralimbic as well as of orbitofrontal regions in BPD.

Amygdala

Previous research findings highlighted the key role of the amygdala for the understanding of BPD, especially with regard to stronger emotional responding commonly observed in patients with BPD. Along these lines, a multitude of neuroimaging studies provided consistent evidence for neurobiological alterations in the amygdala at the functional, metabolic, and structural level (e.g., Hoerst, et al., 2010; New, et al., 2007; Nunes, et al., 2009; Silbersweig, et al., 2007).

The findings of Study 1 and 3 further corroborate the assumption of enhanced limbic activity in BPD compared to healthy controls. Interestingly, enhanced activity of the limbic system was exclusively observed for the left amygdala. Neuroimaging studies suggest the left and right amygdala to exhibit different functions. The left amygdala is thought to be primarily involved in the conscious processing of emotions and to be based on reflective processes, whereas the right amygdala is stronger implicated in automatic processing of emotions (e.g., Dyck, et al., 2011; Glascher & Adolphs, 2003; Morris, et al., 1998). For instance, Morris et al. (1998) have found lateralized activation of the amygdala to be a result of participants' level of awareness. Subliminal presentation of fearful facial expressions elicited stronger neural activity in the right amygdala. In contrast, supraliminal presentation resulted in enhanced activation of the left amygdala. Thus, one might speculate that enhanced activations of the left amygdala in BPD are primarily a consequence of reflective processes. In other words, the observation of stronger left-lateralized amygdala activations (see Study 1 and 3) might reflect more negative appraisals of the presented stimuli. In fact,

current evidence in BPD illustrated either enhanced activity of the left or of the bilateral amygdala. However, to the best of my knowledge, none of the available studies showed exclusively enhanced activation of the right amygdala in the context of emotional stimuli. Future studies might address the question whether BPD patients show also enhanced activity of the amygdala under conditions of limited visual awareness.

The speculation of a bias towards more negative appraisals in BPD reflected at the neural level fits with recent findings that suggest a negativity bias in the perception of facial emotional expressions (Domes, et al., 2009) as well as with typical BPD cognitions in terms of seeing the world and other people as dangerous (Arntz, et al., 2004; Pretzer, 1990; Renneberg, Schmidt-Rathjens, Hippin, Backenstrass, & Fydrich, 2005; Renneberg & Seehausen, 2010). Appraisal processes might furthermore help to explain why BPD patients do not only show enhanced amygdala activity to the presentation of negative, but also during the processing of neutral stimuli in Study 1. Consequently, future research should investigate whether enhanced activity of the limbic system in BPD is still present under experimental conditions that restrict the degree of conscious processing and related appraisal processes, for instance by using backward-masking paradigms. Enhanced limbic activity to neutral stimuli might be alternatively a consequence of altered anticipation processes in BPD. The anticipation of upcoming events is an important part of antecedent-focused emotion regulation strategies and was previously shown to modulate limbic activity (Abler, Erk, Herwig, & Walter, 2007; Nitschke, et al., 2006). Thus, the presentation of mainly negative pictures in the first study might have led BPD patients to anticipate the onset of negative stimuli more strongly.

Insular cortex

The results of Study 1 additionally highlighted altered functioning of the insular cortex in the processing of emotions in BPD. So far, most functional imaging studies of emotion processing in BPD focused on limbic structures, although functional alterations of paralimbic structures were previously reported in response to unresolved aversive life events (Driessen,

et al., 2009), to the presentation of negative and neutral stimuli (Koenigsberg, Siever, et al., 2009; Niedtfeld, et al., 2010), or during automatic memory retrieval (Schnell, Dietrich, Schnitker, Daumann, & Herpertz, 2007). Additional findings were provided by a socio-economic game approach that reported altered functioning of the insular cortex in the context of cooperation and norm violation (King-Casas, et al., 2008). Structural analyses yielded no group differences in gray matter volumes of the insular cortex, although insular volume in teenagers with first-presentation BPD was negatively associated with impulsive and violent behavior (Takahashi, et al., 2009).

To date, it would be premature to draw definite conclusions about insular alterations in BPD, for instance the reported coordinates of neurofunctional alterations vary substantially from anterior to posterior parts of the insula. However, the insular cortex seems to play a crucial role across a variety of processes closely associated with the psychopathology of BPD. Hence, it could be argued that future studies should determine the extent of neurobiological alterations at functional, metabolic, and structural levels of the insula to improve the understanding of BPD.

For example, the insular cortex is predominantly implicated in the integration of multimodal information, particularly bodily states (Critchley, 2009). Therefore, a combination of functional neuroimaging with autonomic measures might prove particularly useful to investigate neural representations of bodily states in BPD in order to elucidate states of aversive tension in BPD. This symptom refers to subjective experiences of bodily arousal without a further differentiation of distinct emotions (e.g., Stiglmayr, et al., 2001). It is known that states of tension occur more frequently in BPD and are experienced as highly aversive (Stiglmayr, et al., 2005; Stiglmayr, et al., 2001). Since the insula has a predominant role in the representation of bodily states and widespread anatomic connections to prefrontal and limbic structures, insular cortices are also critically positioned to mediate the processing of pain (for a review, see Rainville, 2002). Pain sensitivity was consistently found to be reduced in BPD (e.g., Bohus, et al., 2000; Schmahl, et al., 2006; Schmahl, Greffrath, et al., 2004), although patients have no impairments in the detection or discrimination of sensory stimuli

(Ludaescher, et al., 2007; Schmahl, Greffrath, et al., 2004). Most importantly, states of aversive tension were found to result in a further decline of pain sensitivity (Bohus, et al., 2000; Ludaescher, et al., 2007) and to trigger the urge to engage in self-injurious behavior (Herpertz, 1995; Stiglmayr, et al., 2005; Stiglmayr, et al., 2001). Thus, it seems intriguing to hypothesize that neurofunctional alterations of the insular cortex might cause symptoms of aversive tension and altered pain processing in BPD.

Finally, the insular cortex was found to be involved in emotion processing (Kober, et al., 2008), empathy (Singer, et al., 2004), as well as decision making and fairness (Kuhnen & Knutson, 2005; Sanfey, Rilling, Aronson, Nystrom, & Cohen, 2003). The overlapping activations across these widespread contexts might result from specific involvements of the insular cortex in the processing of emotions related to social interactions (Lamm & Singer, 2010). Deficits in the maintenance and quality of social relationships are highly characteristic for all personality disorders (Rutter, 1987). Accordingly, BPD patients report highly ambivalent relationships (Stepp, Pilkonis, Yaggi, Morse, & Feske, 2009) and more interpersonal conflicts (Clifton, Pilkonis, & McCarty, 2007). They show diminished trust (Unoka, Seres, Aspan, Bodi, & Keri, 2009) and have difficulties in the understanding of the intentions and emotions of other people (Preissler, et al., 2010). Remarkably, impairments in emotional empathy, i.e., emotional responses to observed emotional states of other people (Blair, 2005), were associated with enhanced activation of insular regions in BPD (Dziobek, et al., in press).

Orbitofrontal cortex

In addition to alterations in limbic regions, the previously presented results provide support for a dysfunctional prefrontal network in BPD. In particular, patients showed attenuated activations of the left orbitofrontal cortex during their attempts to decrease the initial emotional response by means of cognitive reappraisal (see Study 1). In line with this finding, decreased activity of the orbitofrontal cortex was also reported when patients performed an emotional go/no-go task (Silbersweig, et al., 2007). Furthermore, connectivity analyses have

reported a resting-state disconnection of orbitofrontal and limbic regions in BPD (New, et al., 2007).

Orbitofrontal regions are consistently implicated in the neural representation of cognitive reappraisal and represent an important node of the widespread prefrontal network underlying emotion regulation. Critically, the strength of functional coupling between the orbitofrontal cortex and the limbic system was found to mediate successful reappraisal (Banks, et al., 2007). Additional findings associate the orbitofrontal cortex with stimulus-reinforcement learning and the processing of the contextual relevance of stimuli (for a review, see Rolls, 2004). Thus, recruitment of the orbitofrontal cortex during cognitive reappraisal might be best understood by a reversal of the previous appraisal (Ochsner, et al., 2004). The importance of the orbitofrontal cortex in emotion regulation is highlighted when considering that everyday interactions are characterized by rapidly changing contexts that require flexible responding (Rempel-Clower, 2007).

Interestingly, a recent meta-analysis reported a shift of neural activations from left to right and posterior to anterior when participants had more time to reappraise (Kalisch, 2009). The author concluded that early and late phases of reappraisal differ in their neural representation and proposed a temporal model of reappraisal. Early phases reflect the implementation of reappraisal, whereas later phases reflect the maintenance and the monitoring of the effects of reappraisal on emotional responses. In line with this model, one might conclude that the strong left-lateralized attenuated functioning of the orbitofrontal cortex in BPD illustrate pronounced deficits in the implementation of reappraisal strategies to regulate emotions.

Taken together, the presented results further underline neurobiological alterations in the processing and regulation of emotions in patients with BPD. Previous research and the findings presented in this thesis specifically implicate altered functioning of limbic and paralimbic regions along with attenuated functioning of prefrontal cortices. The general state

of research regarding neurofunctional alterations in the generation and regulation of emotions in BPD is presented in Figure 5.1.

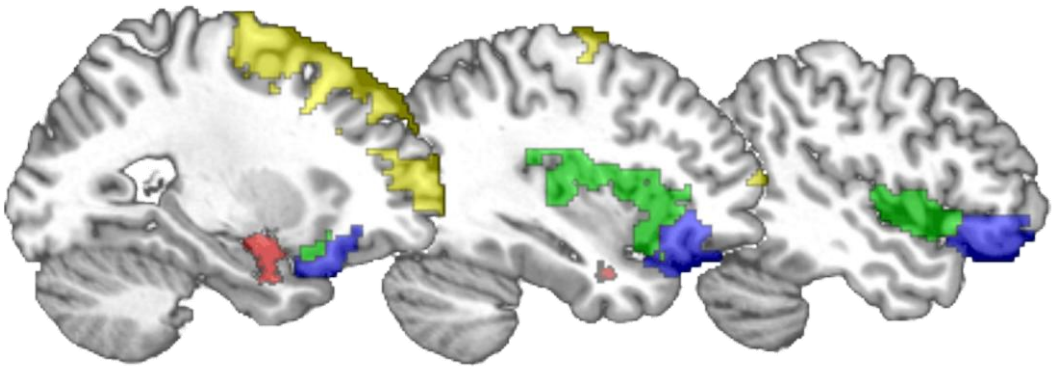

Figure 5.1. **Neurofunctional alterations in the generation and regulation of emotions in BPD.** Enhanced neural activity in the amygdala (red) as well as insular cortex (green) of BPD patients are commonly reported and were proposed to be neural substrates of altered emotional responding. The insular cortex was furthermore implicated in disturbed social interactions of BPD patients. Attenuated activations of the orbitofrontal (blue) and dorsolateral prefrontal cortex (yellow) probably reflect deficits in the explicit and implicit regulation of emotions. Empirical evidence for alterations in the depicted neural networks is presented throughout the thesis. (see also, Herpertz, 2011)

Implications for Models of Emotional Instability in BPD

The studies of this thesis were integrated into a theoretical framework of emotion and emotion regulation to further differentiate emotional difficulties in patients with BPD, thereby allowing to deduce several interesting research questions. The implications of the presented findings for theoretical conceptualizations of emotional instability in BPD will be summarized in the following.

At the beginning of this section, it needs to be pointed out that the results of Study 1 provide crucial support for two-factorial models that suggest emotional instability in BPD to be a result of stronger emotional responding as well as an impaired ability to regulate emotions. In the first study, patients with BPD were characterized by a) enhanced emotional responding and b) impaired implementation of cognitive reappraisal to decrease negative emotions. Importantly, deficits in the use of cognitive reappraisal in this study cannot be accounted for by initially enhanced emotional responses as the maintenance of initial negative emotions served as a baseline condition in the neuroimaging analysis (see Chapter 2). Therefore, emotional difficulties in BPD currently summarized as emotional instability, for instance in the recent version of the DSM, seem to be the result of two distinct processes.

Emotion generation

The first factor of emotional instability, i.e., enhanced emotional responding, is consistently illustrated by enhanced activation of neural networks implicated in emotion processing. Considering the modal model of emotion by Gross and Thompson (2007), several factors might underlie stronger emotional responding in BPD. In particular, more negative appraisals as outlined in the previous section and altered attentional orienting might help to explain the generation of stronger emotional responses. Accordingly, a recent study illustrated stronger attentional orienting to negative emotional stimuli in adolescent patients with BPD (von Ceumern-Lindenstjerna, et al., 2010b). However, a clinical control group of patients with other mental disorders showed a similar negative bias in initial attentional orienting. Thus, the

authors suggested that alterations in initial attentional processes might be not specific for patients with BPD (von Ceumern-Lindenstjerna, et al., 2010b).

The hypothesis of more negative appraisals as an explanation for stronger emotional responding in BPD, as discussed in the previous section, might seem plausible. However, similar valence and arousal ratings of the presented stimuli in neuroimaging paradigms were consistently reported and thus question the interpretation that alterations in appraisal processes underlie enhanced emotional responses. Nevertheless, it should be carefully considered that patients with BPD have severe difficulties to label their emotional reactions (Linehan, 1993, 1995) and also provide more variable ratings compared to healthy controls in the assessment of emotional stimuli (Koenigsberg, Fan, et al., 2009).

Taken together, to date, only limited evidence is available for alterations of attention and appraisal processes in BPD that might help to understand the generation of stronger emotional responses. Future investigations are consequently needed to determine if BPD is characterized by alterations in attention and appraisal processes and how these presumed alterations relate to emotional responding. Alternatively, stronger emotional reactions might be due to disturbed functioning of the componential response system in BPD. In other words, similarly attended and appraised situations might result in more drastic changes of subjective experiences, cognitions, and physiological states in BPD patients compared to non-clinical groups.

Emotion regulation

Deficits in the regulation of emotions represent the second factor assumed to underlie emotional instability in BPD. As outlined in Chapter 1, several facets of emotion regulation have been proposed that directly refer to the time course of the generation of emotional responses. Thus, deficiencies if the use of these strategies may additionally affect the strength of emotional responding in BPD. In the following, I will discuss evidence for deficits in these specific emotion regulation strategies.

The selection and modification of situations represent the earliest possibilities to alter the intensity or quality of emotions. The use and effects of these strategies were neither in previous research nor in the studies of this thesis explicitly investigated, although psychotherapists commonly observe that BPD patients report to find themselves more often in “dysfunctional situations” that are strongly associated with negative emotions. Enhanced traits of sensation seeking might be one explanation. However, previous research has found no differences between healthy controls and BPD patients in sensation seeking (Jacob, et al., 2010; Norra, et al., 2003). Further research is needed to investigate regulatory strategies of situation selection and modification, especially with regard to the anticipated emotional outcome of upcoming situations in patients with BPD.

The attentional selection of situational aspects is closely linked to subsequent emotional responses. Attentional deployment defines consequently a strategy that changes the attentional focus to regulate the generation of emotions. The effects of this particular strategy were reported in Chapter 3 and Chapter 4. The presented findings suggest that modulations of attentional resources due to the engagement in a secondary cognitive task exhibit comparable inhibitory influences on emotional responding in healthy controls and BPD patients. In other words, both groups showed a similar decline of limbic activity by manipulations of working memory load. Consequently, the use of attentional deployment strategies for the regulation of emotions might prove particularly useful to attenuate the extent of emotional responding in BPD. This assumption is further strengthened by previous suggestions that the effects of self-injurious behavior might also be explained in terms of attentional deployment. In particular, it was suggested that the self-inflicted pain could serve as a particularly powerful (albeit highly dysfunctional) strategy to deploy attentional resources from the processing of emotions (Niedtfeld, et al., 2010). Importantly, studies 2 and 3 investigated the effects of an on-going engagement in a secondary task on emotional responding. Previous research findings suggested that patients with BPD, although not characterized by a bias in the initial focus of attention, have specific difficulties in the automatic disengagement of attentional resources from facial expressions (von Ceumern-

Lindenstjerna, et al., 2010a). Thus, deficits in the automatic use of attentional deployment strategies might substantially contribute to the strength of emotional responding in BPD.

Cognitive reappraisal represents the most important form of cognitive change and a highly interesting facet of emotion regulation. In the first study of this thesis (see Chapter 2), patients were found to be characterized by difficulties in the implementation of alternative appraisals of the presented stimuli. This finding directly concurs with a recent report by Koenigsberg et al. (2009), who investigated the effects of cognitive distancing on emotions in BPD and reported attenuated activations of the ventrolateral prefrontal cortex, previously found to crucially mediate the success of reappraisal (Wager, et al., 2008). Thus, convergent evidence suggests deficient effects of reappraisal as a strategy to alter emotional responses in BPD. The results of the first study further suggest that the deficits in the use of reappraisal might be restricted to the attenuation of negative emotions, as both groups showed comparable neural patterns during the increase of initially elicited emotions. Importantly, future research is needed to disentangle the open question, whether patients are primarily characterized by deficits in the implementation and formulation of alternative appraisals or the maintenance of reappraisal (Kalisch, 2009). The analysis of time courses of cognitive reappraisal as well as experimental comparisons of different reappraisal strategies might provide valuable suggestions to establish reappraisal strategies in therapeutic contexts.

Notably, the aforementioned strategies directly aim to alter the generation of emotions and might thus affect the strength of emotional responding in BPD. In contrast, emotion suppression is used to change the expression of emotions, whereas the intensity or qualities of the emotions are not targeted by this regulation strategy. In line with additional research findings, it was therefore proposed that emotion suppression might have negative effects on mental health (John & Gross, 2004). The effects of emotion suppression on negative and positive affect were subject of an experience sampling study in students high or low in BPD features (Chapman, Rosenthal, & Leung, 2009). Surprisingly, suppression of emotional expressions was found to increase positive affect and decrease impulsive behavior in students high in BPD features. However, this result requires further investigation, especially

with regard to the long-term effects. Emotion suppression is one facet of experiential avoidance that implies an unwillingness of a person “to remain in contact with particular private experience (e.g., bodily sensations, emotions, thoughts, memories, behavioral predispositions) and takes step to alter the form or frequency of these events and the contexts that occasion them” (Hayes, Wilson, Gifford, Follette, & Strosahl, 1996, p.1154). Experiential avoidance was found to be associated with self-injurious behavior (Chapman, Specht, & Cellucci, 2005).

This section aimed to illustrate the implications of the findings in this thesis for the understanding of emotional instability in BPD. In short, the results add further support for enhanced emotional reactivity as well as of circumscribed deficits in the regulation of emotions in patients with BPD. Thus, two-factorial models should be considered to replace the common broad classification of emotional difficulties in BPD as emotional instability. The integration of recent BPD findings in theoretical models of emotion generation and emotion regulation additionally highlighted the need to further investigate specific facets of these processes. Future research on two-factorial models might help to advance therapeutic concepts for the treatment of BPD.

Limitations and Future Directions

The current findings hold some limitations that will be addressed in the following section.

First, although impairments in the regulation of emotions are highly characteristic for patients with BPD, they are also postulated for a wide range of mental disorders (Gross & Levenson, 1997). Future research should therefore address whether the findings presented in this thesis are specific for BPD. Alternatively, deficits in the regulation of emotions might be investigated based on a dimensional understanding of personality disorders. The correlation analyses presented in Chapter 2 suggest that self-reported deficits in emotion regulation are strongly associated with the neural results across the sample of BPD patients and healthy controls. Thus, dimensional investigations of personality traits and their association with the generation and regulation of emotions may add important information for the understanding of personality disorders. The importance of dimensional approaches for the understanding of personality disorders is also reflected in current diagnostic developments. Recent proposals for revisions of the diagnostic assessment of personality disorders in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) include a change to a hybrid model that combines categorical and dimensional approaches (Personality and Personality Disorders Work Group, 2011).

Second, it is commonly suggested that BPD patients' difficulties arise from neurofunctional alterations of a fronto-limbic network (P. A. Johnson, et al., 2003). However, the functional and structural connectivity of prefrontal and limbic regions in BPD is to date mostly unknown. New et al. (2007) report a disconnection of the prefrontal cortex and limbic regions during resting states in BPD and additional evidence for altered functional connectivity in resting-state networks of BPD patients was recently provided (Wolf, et al., in press). Additional observations suggest that painful sensory stimulation increases the inhibitory coupling of prefrontal and limbic regions in BPD, thereby helping to understand the soothing effects of self-injurious behavior at the neurobiological level (Niedtfeld, et al., unpublished observations). Future investigations of neural networks using independent

component analyses as well as of functional or effective neural connectivity might consequently help to refine whether neurobiological alterations of a fronto-limbic network are characteristic for BPD.

Third, direct comparisons of different emotion regulation strategies might provide important information for the advancement of therapeutic concepts. Two recent studies compared the effects of cognitive distraction and cognitive reappraisal on emotions (Kanske, Heissler, Schonfelder, Bongers, & Wessa, 2011; McRae, et al., 2010). Cognitive distraction and reappraisal decreased negative affect and limbic activity, and both relied on neural networks that comprise medial and dorsolateral prefrontal structures as well as parts of the parietal cortex. Further statistical comparisons also highlighted a stronger efficacy of cognitive distraction in the attenuation of amygdala activity compared to cognitive reappraisal (Kanske, Heissler, Schonfelder, Bongers, & Wessa, in press; McRae, et al., 2010). Whereas cognitive reappraisal more strongly activated the orbitofrontal cortex and middle frontal gyrus, cognitive distraction activated the superior parietal cortex. Thus, these results point to the potential importance to therapeutically target distraction techniques in patients characterized by deficits in the regulation of emotions.

Fourth, developmental aspects of generation and regulation of emotions might be crucial to understand why BPD mostly emerges in adolescence. This developmental phase is particularly characterized by heightened emotional reactivity and deficits in the regulation of emotions (Arnett, 1999). Adolescents were found to exhibit enhanced limbic activity to emotional stimuli in comparison to children or adults (Ernst, et al., 2005; Hare, et al., 2008; Monk, et al., 2003), and prefrontal maturation was shown to last until the early 20s (Giedd, 2004). Adolescents were found to have a deficient top-down control, which is especially evident in emotional contexts (Eshel, Nelson, Blair, Pine, & Ernst, 2007; Galvan, et al., 2006). Since developmental aspects demand further investigation, the biosocial developmental model of BPD could offer a suitable framework to deduce specific hypotheses (Crowell, Beauchaine, & Linehan, 2009).

Fifth, it might be of interest to investigate the role of emotional labeling. Patients with BPD are suggested to be characterized by deficits in the labeling of their emotions (Linehan, 1993). This proposal directly concurs with findings of emotion recognition tasks that require patients to use verbal labels to accurately describe emotional states of other persons (e.g., Domes, et al., 2008; Dyck, et al., 2009). In these tasks, patients were found to be characterized by impairments in the recognition of emotional states (for a review, see Domes, et al., 2009), thereby contradicting the presumption of enhanced emotional sensitivity (Linehan, 1995). However, recent results provide empirical support for differences in semantic representation of emotions in BPD (Suvak, et al., in press). Consequently, impairments in emotion recognition tasks might rather reflect deficits in the access of semantic labels to describe emotional states. In addition, accurate labeling of emotions was found to diminish amygdala activity in healthy controls and is probably concerted by enhanced activity of the right ventrolateral prefrontal cortex (Hariri, Bookheimer, & Mazziotta, 2000; Lieberman, et al., 2007). This specific region of the prefrontal cortex is commonly suggested to mediate the effects of cognitive reappraisal (Wager, et al., 2008). Theoretical support for associations of emotional labeling and reappraisal emerge when considering the chronological sequence of cognitive reappraisal. Prior to being able to cognitively reappraise a situation, individuals first have to label their emotional response and to understand the appraisal underlying the generated emotions. Only then, individuals are able to develop alternative appraisals that are further used for self-verbalized regulation of emotions. Thus, impairments in the effects of cognitive reappraisal in BPD might be related to impairments in labeling of emotional states. Future investigations of emotional labeling might add important findings for the understanding of emotion processing and emotion regulation in BPD.

Finally, in the presented studies either female (Chapter 2) or male (Chapter 3 and 4) participants were investigated. Although, by this means, gender influences in the processing (for a meta-analysis see, Wager, Phan, Liberzon, & Taylor, 2003) and regulation of emotions (Domes, et al., 2010; McRae, Ochsner, Mauss, Gabrieli, & Gross, 2008) were avoided, future research is needed to evaluate whether the results of this thesis apply for BPD patients in

general. The results of a previous study suggest that male and female patients with BPD differ at a metabolic level in response to a serotonergic challenge (Soloff, Meltzer, Becker, Greer, & Constantine, 2005) and those differences were found to be furthermore related to impulsive aggression. Thus, future research is encouraged to determine the effects of gender in BPD and the relation of this factor to differences in psychopathology and personality traits (Skodol & Bender, 2003).

The final section of this chapter aimed to highlight several potential routes for future research in patients with BPD, which might aid the advancement of therapeutic concepts for the treatment of BPD.

Summary

Chapter 6

Borderline personality disorder is a highly prevalent Axis-II disorder in clinical contexts and characterized by a pervasive pattern of instability in several domains. In particular, emotional instability was proposed to be highly characteristic for patients with BPD and furthermore shown to be directly related to many symptoms of BPD patients, e.g., self-injurious behavior, feelings of chronic emptiness, or interpersonal impairments. Emotional instability was proposed to be caused by enhanced emotional responding and deficits in emotion regulation. The central role of emotional instability for the understanding of BPD was the starting point of the studies presented in this thesis with the aim to differentiate deficits in the regulation of emotions. Two different strategies (i.e., cognitive distraction and cognitive reappraisal) to modulate emotions as well as their neurobiological correlates in BPD were investigated.

Cognitive reappraisal is a well-known strategy to regulate emotions and refers to a re-evaluation of the appraisal of a situation. The effects of this particular emotion regulation strategy were investigated in the first study. A delayed reappraisal paradigm was used that comprised an initial viewing phase followed by an instruction cue to modulate the personal relevance of the presented stimuli. By this means, the paradigm allowed to distinguish emotional reactivity and cognitive reappraisal in BPD. Participants were asked to either decrease, increase, or maintain the elicited emotional responses. Statistical analyses of the initial phase illustrated limbic and paralimbic hyperactivity during the presentation of negative and neutral stimuli in BPD compared to healthy controls. With regard to the regulatory phase, cognitive reappraisal was found to result in enhanced activations of a prefrontal network consisting of orbitofrontal, dorsolateral and medial prefrontal regions. Apart from prefrontal regions, parts of the anterior cingulate cortex modulated the neural activity of limbic and paralimbic regions in accordance with the regulatory goal. Further comparisons of BPD patients with healthy controls illustrated attenuated activations of the orbitofrontal cortex

along with less reduced neural activity in the bilateral insula during the decrease of emotional reactions in BPD patients. The results thereby provide further support for two distinguishable processes that underlie emotional difficulties in BPD, i.e., enhanced emotional responding and impairments in the cognitive regulation of emotions. Importantly, no further differences between BPD patients and healthy controls were found in regions associated with the processing or regulation of emotions when participants attempted to increase their negative emotions.

Cognitive distraction represents an important form of attentional deployment and refers to the engagement in a secondary task while being confronted with an emotional stimulus. The effects of cognitive distraction on emotional responses in BPD were addressed in a subsequent study. Since, there is considerable controversy regarding the effects of attentional resources on emotion processing (for a discussion, see Chapter 1), the consequences of manipulations of cognitive resources on emotion processing were initially evaluated in a sample of healthy participants. In this study, cognitive resources were manipulated via two different levels of working memory demands. While participants engaged in the working memory task, social scenes of varied emotional saliency were additionally presented in the background. Increased working memory demands resulted in enhanced activation of a fronto-parietal network and were found to attenuate activity of the bilateral amygdala in general. Additional analyses suggested the dampening effects of working memory load on limbic activity to be mediated by the bilateral dorsolateral prefrontal cortex.

The observed effects of reduced cognitive resources on limbic processing encouraged an investigation of this specific emotion regulation strategy in BPD. Thus, the third study investigated the interaction of cognitive and emotional processes in individuals primarily characterized by affective instability, i.e. male criminal offenders with antisocial personality disorder and BPD. Importantly, healthy controls and criminal offenders did not differ in their general task performance or neural representation of working memory

processes when no distracting stimuli were presented in the background of the working memory task. However, the additional presentation of highly salient emotional stimuli was associated with prolonged reaction times and enhanced activation of the left amygdala in criminal offenders characterized by emotional instability compared to control participants. Interestingly, behavioral interference and emotional reactivity were found to be independent of working memory load. In other words, although BPD participants were characterized by enhanced limbic activity to highly salient stimuli in general, both groups showed comparable attenuations of limbic activity by cognitive load. The comparable effects of cognitive distraction on emotion processing in criminal offenders with BPD and healthy controls suggest that attentional deployment strategies are useful to attenuate emotional responses in BPD and support recent therapeutic concepts that aim to establish distraction techniques for the regulation of emotions.

To summarize, the findings of this thesis provide support for enhanced emotional responding as well as circumscribed deficits in the cognitive regulation of emotions in patients primarily characterized by affective instability. In particular, the results suggest impairments in the use of cognitive reappraisal strategies to decrease negative emotions, whereas no significant differences between BPD patients and healthy controls were found in the effects of cognitive distraction. Furthermore, the findings of this thesis implicate neurofunctional alterations in limbic and paralimbic regions paralleled by attenuated functioning of the orbitofrontal cortex to be associated with emotional difficulties in BPD.

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Zusammenfassung

Die Borderline-Persönlichkeitsstörung (BPS) ist vorrangig durch Instabilität in den Bereichen Affekt, Verhalten, Selbstbild und zwischenmenschlichen Beziehungen gekennzeichnet. Das Symptomcluster der BPS geht einher mit schwerwiegenden Einschränkungen im psychosozialen Funktionsniveau. Infolgedessen stellen BPS Patienten eine der größten Gruppe einer spezifischen Persönlichkeitsstörung in ambulanten und stationären Therapieeinrichtungen dar. Aktuelle Modelle betonen insbesondere die zentrale Rolle der affektiven Instabilität für das Verständnis des Störungsbildes, wobei empirische Untersuchungen direkte Zusammenhänge mit selbstverletzenden Verhalten, Gefühlen chronischer Leere und Defiziten in interpersonellen Beziehungen nachweisen konnten. Gegenwärtig wird übereinstimmend davon ausgegangen, dass die affektive Instabilität von BPS Patienten eine Konsequenz erhöhter emotionaler Reagibilität sowie von Defiziten in der Regulation von Emotion ist. Die grundlegende Rolle affektiver Instabilität bei BPS motivierte die Studien der vorliegenden Arbeit, welche vorrangig darauf abzielten, postulierte Defizite in der Emotionsregulation bei BPS differenzierter zu betrachten. Hierfür wurden die Auswirkungen kognitiver Ablenkung sowie kognitiver Neubewertung - zwei verbreiteten Regulationsstrategien – untersucht. Die durchgeführten Untersuchungen beschäftigten sich insbesondere mit den neurofunktionellen Korrelaten der genannten Emotionsregulationsstrategien.

Die Neubewertung von emotionsauslösenden Situationen stellt eine bekannte Regulationsstrategie dar. Fertigkeiten zur Neubewertung von emotionsauslösenden Situationen werden unter anderem in kognitiv-verhaltenstherapeutischen Therapieverfahren vermittelt. Die Auswirkungen kognitiver Neubewertung zur Regulation der ausgelösten emotionalen Reaktionen wurden in Studie 1 untersucht. Den Probanden wurden hierfür negative und neutrale Bilder präsentiert, gefolgt von einer Instruktion die ausgelöste Reaktion zu vermindern, zu verstärken oder beizubehalten. Auf diese Weise ermöglichte das

experimentelle Paradigma die Stärke ausgelöster emotionaler Reaktionen sowie die Effekte kognitiver Neubewertung getrennt zu analysieren. Bei der initialen Betrachtung negativer und neutraler Stimuli ergaben die statistischen Auswertungen eine verstärkte Aktivierung limbischer und paralimbischer Reaktionen bei Patientinnen mit BPS im Vergleich zu gesunden Kontrollprobandinnen. Die Neubewertung der negativen Stimuli war mit einem Anstieg der neuronalen Aktivität innerhalb eines präfrontalen Netzwerkes, bestehend aus Teilen des orbitofrontalen und des anterioren cingulären Kortex, sowie Regionen des dorsolateralen und medialen präfrontalen Kortex assoziiert. In Abhängigkeit der Richtung der Neubewertung konnten modulierende Einflüsse auf die Aktivität limbischer und paralimbischer Strukturen nachgewiesen werden. Statistische Vergleiche zwischen BPS Patientinnen und Kontrollprobandinnen verdeutlichten eine verminderte Aktivierung des orbitofrontalen Kortex bei der Abschwächung der ausgelösten emotionalen Reaktion bei Patientinnen mit BPS, welche weiterhin mit einer erhöhten Aktivität der Insula einherging. Die Ergebnisse verdeutlichen, dass sich emotionale Schwierigkeiten bei BPS durch zwei voneinander trennbare Prozesse erklären lassen. Patientinnen mit BPS zeigen sowohl eine erhöhte emotionale Reagibilität als auch Schwierigkeiten bei der Regulation von Emotionen. Allerdings ergaben sich keine Unterschiede zwischen BPS Patientinnen und Kontrollprobandinnen in neuronalen Strukturen, die mit der Verarbeitung und Regulation von Emotionen assoziiert sind, wenn Patientinnen dazu aufgefordert wurden, die initiale Reaktion zu verstärken. Schwierigkeiten in der Regulation von Emotionen sind somit möglicherweise auf die Abschwächung von negativen Emotionen beschränkt.

Kognitive Ablenkung stellt eine weitere Form der Emotionsregulation dar und bezieht sich auf die Beschäftigung mit einer ablenkenden Aufgabe, während die Person mit emotionalen Reizen konfrontiert wird. Die Auswirkungen kognitiver Ablenkung wurden in einer Folgestudie untersucht. Allerdings ist gegenwärtig strittig, welche Auswirkung die Manipulation kognitiver Ressourcen auf die Verarbeitung von emotionalen Stimuli hat (siehe Kapitel 1). Infolge der aktuellen Diskussion zur Ab- bzw. Unabhängigkeit der Verarbeitung emotionaler Reize von kognitiven Ressourcen wurden die Effekte kognitiver Ablenkung

zuerst in einer Stichprobe ohne psychopathologische Auffälligkeiten untersucht. Im Rahmen dieser zweiten Studie wurden die kognitiven Ressourcen der Probanden durch eine Arbeitsgedächtnisaufgabe mit zwei verschiedenen Schwierigkeitsgraden manipuliert. Während die Probanden diese Aufgabe bearbeiteten, wurden parallel im Hintergrund soziale Szenen in variierter emotionaler Salienz präsentiert. Verstärkte Anforderungen an das Arbeitsgedächtnis gingen mit erhöhten Aktivierungen innerhalb eines präfrontalen-parietalen Netzwerkes einher und resultierten in einer generellen Abschwächung der bilateralen Amygdala-Aktivität. Zusätzliche Analysen ergaben, dass der abschwächende Effekt auf die limbische Aktivität insbesondere durch den dorsolateralen präfrontalen Kortex vermittelt wurde.

Infolge der Verringerung limbischer Aktivität durch die Manipulation kognitiver Ressourcen wurde diese Emotionsregulationsstrategie ebenfalls bei Personen mit hoher affektiver Instabilität untersucht. Hierfür wurden Straftäter mit antisozialer Persönlichkeitsstörung sowie BPS rekrutiert. Kontrollprobanden und affektiv instabile Straftäter unterschieden sich weder in der Performanz noch in der neuronalen Repräsentation von Arbeitsgedächtnisprozessen, solange keine ablenkenden visuellen Stimuli präsentiert wurden. Die zusätzliche Präsentation emotionaler Stimuli hoher Salienz ging mit einer Verlängerung der Reaktionszeiten bei affektiv instabilen Straftätern einher. Zusätzlich konnte auf neuronaler Ebene bei dieser Bedingung eine verstärkte Aktivierung der linken Amygdala nachgewiesen werden. Interessanterweise waren beide Effekte unabhängig von der Belastung des Arbeitsgedächtnisses. Dieser Befund verdeutlicht, dass sich bei beiden Gruppen eine vergleichbare Abschwächung der neuronalen Aktivität in der Amygdala infolge erhöhter Anforderungen an das Arbeitsgedächtnis zeigte. Die vergleichbaren Effekte kognitiver Ablenkung auf die Verarbeitung emotionaler Stimuli verdeutlichen, dass die Beschäftigung mit einer ablenkenden Aufgabe eine nützliche Form der Emotionsregulation darstellt und bestätigen somit therapeutische Konzepte, die unter anderem Ablenkungstechniken zur Regulation von Emotionen vermitteln.

Zusammenfassend lässt sich feststellen, dass die berichteten Ergebnisse eine grundlegende verstärkte emotionale Reaktion sowie umschriebene Defizite in der Regulation von Emotionen bei affektiv instabilen Personen bestätigen. Die Ergebnisse verdeutlichen insbesondere Schwierigkeiten in der Verwendung von kognitiven Neubewertungsstrategien zur Abschwächung von Emotionen. Es ließen sich hingegen keine signifikanten Gruppenunterschiede in den Auswirkungen kognitiver Ablenkung nachweisen. Darüber hinaus verdeutlichen die durchgeführten Arbeiten, dass die Schwierigkeiten im Umgang mit Emotionen bei BPS im Zusammenhang mit neurofunktionellen Veränderungen der Amygdala und Insula sowie des orbitofrontalen Kortex stehen.

Curriculum Vitae

For reasons of data protection the curriculum vitae in not available in the online version of this dissertation.

Publications

Prehn, K.*, Schulze, L.*, Roßmann, S., Berger, C., Vohs, K., Fleischer, M., Hauenstein, K., Keiper, P., Domes, G., & Herpertz, S.C. (in press). Effects of emotional stimuli on working memory processes in male criminal offenders with borderline and antisocial personality disorder. *World J Biol Psychiatry*. *equally contributing authors

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Selbstständigkeitserklärung

Hiermit versichere ich, dass ich die vorgelegte Arbeit selbstständig verfasst habe und keine anderen als die angegebenen Quellen und Hilfsmittel benutzt wurden, sowie Zitate kenntlich gemacht habe.

Die Arbeit ist in keinem früheren Promotionsverfahren angenommen oder abgelehnt worden.

Berlin, den 16. März 2012 Lars Schulze

Appendix

Publication - Neuronal Correlates of Cognitive Reappraisal in Borderline Patients Characterized by Affective Instability

The appendix has been published as ‘Schulze, L., Domes, G., Krüger, A., Berger, C., Fleischer, M., Prehn, K., Schmahl, C., Grossmann, A., Hauenstein, K. & Herpertz, S.C. 2011. Neuronal correlates of cognitive reappraisal in borderline patients with affective instability. *Biological Psychiatry, 69, 564-73.*’

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Publication - Effects of Emotional Stimuli on Working Memory Processes in Male Criminal Offenders with Borderline and Antisocial Personality Disorder

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