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Review

Emotional sensitivity, emotion regulation and impulsivity in borderline personality disorder: A critical review of fMRI studies



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ABSTRACT

Emotional sensitivity, emotion regulation and impulsivity are fundamental topics in research of borderline personality disorder (BPD). Studies using fMRI examining the neural correlates concerning these topics is growing and has just begun understanding the underlying neural correlates in BPD. However, there are strong similarities but also important differences in results of different studies. It is therefore important to know in more detail what these differences are and how we should interpret these. In present review a critical light is shed on the fMRI studies examining emotional sensitivity, emotion regulation and impulsivity in BPD patients. First an outline of the methodology and the results of the studies will be given. Thereafter important issues that remained unanswered and topics to improve future research are discussed. Future research should take into account the limited power of previous studies and focus more on BPD specificity with regard to time course responses, different regulation strategies, manipulation of self-regulation, medication use, a wider range of stimuli, gender effects and the inclusion of a clinical control group.

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1. Introduction

Borderline personality disorder (BPD) is a severe psychiatric disorder, which affects 1–3% of the general population (Lenzenweger et al., 2007; Trull et al., 2010). The Diagnostic and Statistical Manual of Mental Disorders (DSM-V; American Psychiatric Association, 2013) defines the main features of BPD as a pervasive pattern of instability in interpersonal relationships, emotions, self-image as well as marked impulsive behavior. Furthermore, BPD patients are characterized by repeated self-injury, suicidal tendencies, reactive aggression and high rates of comorbid mental disorders (Leichsenring et al., 2011; Lieb et al., 2004). BPD severely affects employment, and in combination with high use of the mental health care, results in high societal costs (van Asselt et al., 2007).

Leading theories on the etiology of BPD (Crowell et al., 2009; Koenigsberg et al., 2009b; Linehan, 1993) propose that BPD is best understood as an emotion dysregulation disorder, caused by an increased emotional sensitivity and an inability to regulate emotional responses. The inability to regulate emotional responses might consequently result in marked impulsive behavior, characteristic for BPD patients. In the last decades researchers have used different behavioral and psychophysiological methods to test the hypothesized increased emotional sensitivity and diminished regulation (see for reviews Domes et al., 2009; Rosenthal et al., 2008). Results seem inconsistent. In line with the emotion dysregulation hypothesis, several studies show that BPD patients have a stronger emotional reaction to emotional stimuli when compared to non-patient controls (NPC), as indicated by an increased heart rate (Ebner-Priemer et al., 2007; Lobbestael and Arntz, 2010), increased skin conductance responses (Lobbestael and Arntz, 2010), larger startle response (Ebner-Priemer et al., 2005; Hazlett et al., 2007), decreased facial recognition accuracy (Bland et al., 2004; Levine et al., 1997) or a more accurate facial recognition (Lynch et al., 2006; Wagner and Linehan, 1999). In contrast, studies also demonstrated that BPD patients had lower skin conductance responses (Herpertz et al., 1999) and lower levels of endocrine stress markers (Nater et al., 2010) when confronted with emotional stimuli or stressful situations, which seems to indicate lower levels of emotional reactivity. Behavioral data concerning impulsivity in BPD patients are also conflicting. Some studies did not report any differences between NPC and BPD patients during a go/no-go task (Jacob et al., 2010; Vollm et al., 2004), while others showed that BPD patients make significantly more commission errors, indicating that they are worse in response inhibition (Leyton et al., 2001; Mortensen et al., 2010; Rentrop et al., 2008). Taken together, these studies show mixed findings concerning emotional reactivity as well as impulsivity in BPD.

In recent years an increasing number of neuroimaging studies have identified neural correlates associated with BPD (see for reviews Krause-Utz et al., 2014; Mauchnik and Schmahl, 2010). Many of these studies (e.g. Koenigsberg et al., 2009b; Minzenberg et al., 2007; Schulze et al., 2011; Silbersweig et al., 2007) highlighted a characteristic response in the frontolimbic brain network, comprised of an increased limbic activity and decreased prefrontal activity in BPD patients in response to emotional stimuli. As limbic brain areas have generally been associated with emotion detection and generation processes and prefrontal areas with cognitive

control processes (Davidson and Irwin, 1999; Phillips et al., 2003), these findings have been interpreted as being in concordance with the emotional dysregulation hypothesis of BPD. Although there seems to be a concurrence of neural networks among the neuroimaging studies investigating emotional processing in BPD patients, like in behavioral studies also important differences have been observed. This raises questions about the conclusiveness of the results.

This article provides a critical review of fMRI studies investigating emotional sensitivity, emotion regulation and impulsivity in BPD patients. This review starts with a definition of the investigated constructs of emotional sensitivity, emotion regulation and impulsivity, followed by an overview of, to the best of the present authors' knowledge, all here-to-date relevant publications. These publications are then discussed, summarizing important issues that remain unanswered and are suggested to be taken into consideration for future research. Included in this review are original published peer-reviewed articles, wherein authors make direct conclusions about emotional sensitivity, emotion regulation or impulsivity in BPD patients and compared the resulting brain activity to that of NPC. Given that in BPD research often negative stimuli are used, the present review will focus on fMRI studies using negative stimuli.

2. Emotional sensitivity, emotion regulation and impulsivity: definitions

Emotional sensitivity can be defined as a lower threshold to detect or respond to emotional stimuli, or a higher probability of experiencing stimuli as emotional (Carpenter and Trull, 2013; Linehan, 1993). In BPD patients this might lead to hyperawareness to emotional stimuli and more frequent, intense and/or prolonged emotional experiences. Emotion regulation is a broad concept, referring to different methods and abilities that individuals use to influence the experience and expression of their emotions (Gross, 1998, 2007). These different methods can be categorized as either response-focused or antecedent-focused strategies (Gross, 1998, 2007). Response-focused strategies modulate emotional processes which occur late in the emotion generation process. This involves the inhibition of ongoing emotional expressive behavior such as facial expressions (bodily responses). Antecedent-focused strategies modulate emotional processes early in the emotion generation process, before the emotion response tendencies have become activated. The best-known examples of antecedent-focused strategies are attentional deployment (e.g. distraction) and cognitive reappraisal (e.g. distancing and reinterpretation). Cognitive reappraisal is an often studied emotion regulation strategy in BPD patients, that specifically refers to the ability to reinterpret a stimulus or situation (Gross, 1998, 2007).

Summarizing the set of brain areas involved in emotion generation and regulation is plagued by the fact that different authors use different, but also overlapping, sets of brain areas. In this review we follow the model of cognitive control of emotion (MCCE) as proposed by Ochsner et al. (2012). According to this model brain areas involved in emotion generation are the amygdala, ventral striatum, anterior insula and orbitofrontal cortex (OFC). Most frequently demonstrated brain areas showing an increased activity

during emotion regulation of negative emotional stimuli are the dorsolateral prefrontal cortex (dlPFC), ventrolateral prefrontal cortex (vlPFC), dorsomedial prefrontal cortex (dmPFC) and anterior cingulate cortex (ACC) (Ochsner et al., 2002, 2012; Phan et al., 2005). In accordance with the theory of emotional dysregulation in BPD, it is hypothesized that BPD patients show a greater activity in the aforementioned emotion generation brain areas and less activity in the emotion regulation brain areas during the application of emotion regulation strategies compared to NPC.

Impulsivity is a multidimensional concept consisting of a behavioral, cognitive and motivational dimension (Evenden, 1999; Moeller et al., 2001; Sebastian et al., 2013a). The pattern of impulsivity often diagnosed in BPD patients is largely associated within the behavioral domain, including self-injury, reactive aggression, inappropriate anger, substance or alcohol abuse, unprotected sex, excessive spending of money and gambling, shoplifting, uncontrolled eating and reckless driving (American Psychiatric Association, 2013). Accordingly, in present review impulsivity is defined as a predisposition to rapidly and unplanned responses without considering the consequences (Moeller et al., 2001). Additionally, previous studies (Domes et al., 2006; Jacob et al., 2010; Sebastian et al., 2013a) state that impulsivity in BPD is especially evident under extreme emotional states or situations, this is specified as affective or emotional impulsivity. Key brain areas associated with impulsivity (response inhibition) in NPC are the inferior frontal cortex (IFG)/anterior insula, middle temporal gyrus, OFC/ventromedial prefrontal cortex (vmPFC), premotor areas, dlPFC, ACC and inferior parietal cortex (Garavan et al., 1999; Horn et al., 2003; Sebastian et al., 2013b). In agreement with clinically shown marked impulsive behavior, it is hypothesized that BPD patients show less activity in these response inhibition areas compared to NPC.

3. Emotional sensitivity in BPD

To examine emotional sensitivity in BPD patients, two different types of emotional stimuli have commonly been used in BPD fMRI studies so far. These two stimuli are facial expressions and emotional scenes. The first include the presentation of pictures of faces that vary in their emotional expression (e.g. happy, fearful, and angry) and the second presents pictures depicting scenes differing in their emotional content. Two studies used negative memories to examine emotional sensitivity, one of abandonment (Schmahl et al., 2003) and the other of childhood abuse (Schmahl et al., 2004). However, these are PET studies and therefore will be out of focus in current review. The results of the included studies will be discussed in the light of the model of the cognitive control of emotion. For an overview of all results see Table 2.

3.1. Facial expressions

To date, three studies have used stimuli depicting facial expressions to examine emotional sensitivity in BPD patients (Donegan et al., 2003; Guitart-Masip et al., 2009; Minzenberg et al., 2007; Table 1). All three studies used faces from the Ekman and Friesen set (1979), which contains 60 pictures of faces of ten different persons, six women and four men, displaying six different emotions: happy, sad, fearful, surprised, disgusted and angry. However, the facial expressions included, the task instructions and the analysis slightly varied across the three studies. In the study of Donegan et al. (2003) participants were instructed to attend to faces with a fearful, sad, happy or neutral expression. In the analyses, group differences in brain responses for these facial expressions were separately compared to the brain responses during the presentation of a fixation point. Minzenberg et al. (2007) instructed participants to identify

the gender of neutral, fearful and angry faces that were presented. Brain responses to fearful and angry facial expressions were then compared to brain responses to neutral facial expressions. Finally, Guitart-Masip et al. (2009) used an emotional discrimination task, in which participants had to indicate which of two presented faces showed an emotional expression, or which of two lines was oriented vertical. Brain responses during the emotional discrimination trials of happy, fearful, disgust and angry facial expressions were then compared with brain responses during the orientation trials, using three contrasts: all emotional trials vs. orientation trials, positive discrimination (happy faces) vs. orientation trials and negative discrimination (fearful, disgust and angry faces) vs. orientation trials. To examine group differences two of the three studies (Donegan et al., 2003; Minzenberg et al., 2007) conducted a priori region of interest (ROI) analyses on the amygdala, the other study (Guitart-Masip et al., 2009) conducted a whole brain analysis and a post hoc ROI analyses on the amygdala. Moreover, Minzenberg et al. (2007) performed an ACC ROI analysis.

The results of two studies (Donegan et al., 2003; Minzenberg et al., 2007) confirmed the hypothesis of increased emotional sensitivity, showing greater amygdala activity in BPD patients compared to NPC during the presentation of emotional facial expressions; Donegan et al. (2003) showed greater amygdala activity for the BPD patients during the presentation of all three emotional facial expressions (happy, sad and fearful) and even during the presentation of the neutral faces. Interestingly, Minzenberg et al. (2007) found a greater amygdala and lower ACC activity only during the presentation of fearful faces. This amygdala and ACC pattern was reversed for angry faces. Using the emotion discrimination paradigm, Guitart-Masip et al. (2009) could not replicate these differences in amygdala and ACC activity between the BPD and NPC group (Table 2).

At a p -value of 0.05 these three studies had an estimated power below 80% to correctly reject the null hypothesis at a medium ($d=0.5$) or large ($d=0.8$) effect size (Table 1). To detect a very large effect size ($d=1.5$) the power was sufficient (above 80%) for these three studies. Regarding a more strict p -value of 0.01 only Donegan et al. (2003) had a sufficient power of 90% to detect a very large effect size, Minzenberg et al. (2007) was close to having sufficient power (79%) of correctly rejecting the null hypothesis at a very large effect size (Table 1).

3.2. Emotional scenes

So far, eight studies have used emotional scenes to study emotional sensitivity in BPD patients (Table 1). The first fMRI study using this approach (Herpertz et al., 2001) used intermixed social and non-social scenes, six later studies used social emotional scenes only (Goodman et al., 2014; Koenigsberg et al., 2009a,b; Niedtfeld et al., 2010; Schulze et al., 2011) and one study used visual emotional scenes and textual emotional stimuli (Arntz et al., 2015). All studies used pictures selected from a standardized database (e.g. IAPS; Lang et al., 1997). In these studies participants were either instructed to attend to the pictures (Goodman et al., 2014; Herpertz et al., 2001; Schnell and Herpertz, 2007) or to look at the pictures and allow themselves to respond naturally (Arntz et al., 2015; Koenigsberg et al., 2009a,b; Schulze et al., 2011). To examine the emotional sensitivity of the BPD patients, two contrasts were used among the studies: (1) brain responses during looking at negative scenes were compared with looking at neutral scenes (Arntz et al., 2015; Herpertz et al., 2001; Koenigsberg et al., 2009a; Schulze et al., 2011), or (2) brain response during looking at negative scenes were compared to a fixation condition (Koenigsberg et al., 2009b; Niedtfeld et al., 2010). Schnell and Herpertz (2007) and Goodman et al. (2014) did not compare negative scenes with either neutral

Table 1
Sample characteristics and paradigm descriptions of reviewed studies.

Authors	N BPD/NPC	M age BPD/NPC	% female BPD/NPC	Paradigm of interest	Analysis	Power at $p < .05$ for ^a			Power at $p < .01$ for ^b		
						$d = .5$	$d = .8$	$d = 1.5$	$d = .5$	$d = .8$	$d = 1.5$
<i>Emotional sensitivity</i>											
Arntz et al. (2015)	12/12	30/33	100/100	Passive viewing of visual or textual negative, neutral and positive stimuli	ROI amygdala, hippocampus and ACC	.22	.47	.94	.07	.22	.79
Donegan et al. (2003)	15/15	35/35	87/60	Passive viewing of neutral, happy, sad and fearful faces	ROI amygdala	.26	.56	.98	.10	.30	.90
Goodman et al. (2014)	11/11	33/30	82/82	Passive viewing of negative, neutral and positive scenes	ROI amygdala	.20	.43	.92	.07	.20	.74
Guitart-Masip et al. (2009)	10/10	31/31	50/50	Emotional discrimination task of happy, fearful, disgust and angry faces from the neutral face	Whole brain	.19	.40	.89	.06	.17	.68
Herpertz et al. (2001)	6/6	26/27	100/100	Passive viewing of negative and neutral scenes	Whole brain	.12	.24	.65	.03	.08	.35
Koenigsberg et al. (2009a)	18/16	33/32	56/56	Passive viewing of negative and neutral social scenes	Whole brain	.29	.62	.99	.11	.36	.94
Koenigsberg et al. (2009b)	19/17	35/31	37/47	Passive viewing of negative and positive social scenes	Whole brain	.31	.64	.99	.13	.38	.95
Minzenberg et al. (2007)	12/12	30/31	42/50	Gender discrimination task while attending to fearful, angry and neutral faces	ROI amygdala and ACC	.22	.47	.94	.07	.22	.79
Niedtfeld et al. (2010)	20/23	31/27	100/100	Passive viewing of negative and neutral scenes	Whole brain	.36	.72	.99	.16	.47	.98
Schnell and Herpertz (2007)	6/6	24/23	100/100	Passive viewing of negative scenes	Whole brain	.12	.24	.65	.03	.08	.35
Schulze et al. (2011)	15/15	28/25	100/100	Passive viewing of negative and neutral social scenes	Whole brain	.26	.56	.98	.10	.30	.90
<i>Emotion regulation</i>											
Koenigsberg et al. (2009a)	18/16	33/32	56/56	Distancing and passive viewing of negative social scenes	Whole brain	.29	.62	.99	.11	.36	.94
Lang et al. (2012)	14/15	27/25	100/100	Distancing and passive listening of negative verbal stories	Whole brain	.25	.54	.97	.09	.29	.88
Schulze et al. (2011)	15/15	28/25	100/100	Cognitive reappraisal (i.e. reinterpreting) and passive viewing of negative scenes	Whole brain	.26	.56	.98	.10	.30	.90
<i>Impulsivity</i>											
Jacob et al. (2013)	24/23	29/28	100/100	Letter-based go/no-go task after anger and neutral mood induction	Whole brain	.39	.77	1.00	.18	.53	.99
Silbersweig et al. (2007)	16/14	31/24	94/71	Emotional linguistic go/no-go task with general negative and neutral no-go trials	Whole brain	.26	.56	.98	.10	.30	.90
Wingenfeld et al. (2009)	20/20	30/30	70/70	Emotional Stroop task using general negative, individual negative and neutral words	Whole brain	.34	.69	1.00	.14	.44	.97

^a Calculated power at $p < .05$ for medium, large and very large effect sizes (Cohen's d).

^b Calculated power at $p < .01$ for medium, large and very large effect sizes (Cohen's d).

emotional state). In addition, Schulze et al. (2011) and Lang et al. (2012) explored the effects of up-regulation (increase). Therefore, an up-regulation minus look contrast was applied. During up-regulation participants were instructed to imagine that they, or a close relative, were involved in the situation (Schulze et al., 2011) or imagine themselves as the central figure of the story and heighten their feelings of closeness (Lang et al., 2012).

Result showed that application of the emotional down-regulation techniques during the presentation of the negative stimuli, relative to the passive viewing/listening condition of negative stimuli, led to greater activity in emotion generation areas in BPD patients compared to NPC, including the amygdala (Koenigsberg et al., 2009a) and anterior insula (Schulze et al., 2011), whereas activity in the OFC was diminished (Schulze et al., 2011). With regard to brain areas involved in regulation processes, Koenigsberg et al. (2009a) showed in BPD patients compared to NPC less activity in the ACC and greater activity in the dlPFC, whereas Schulze et al. (2011) reported the opposite pattern for both brain areas. In line with Koenigsberg et al. (2009a), Lang et al. (2012) reported a trend toward a diminished activity in the ACC for the BPD patients.

During the up-regulation condition of negative stimuli, relative to the passive viewing/listening condition of negative stimuli, Schulze et al. (2011) found that BPD patients compared to NPC, showed a decreased activity in the ACC and anterior insula. Since they did not find an increased activity in emotional generation and regulatory brain areas during up-regulation, they stated that emotional dysregulation in BPD patients might be exclusive to down-regulation. In contrast to these results, Lang et al. (2012) did find less activity in regulation associated brain areas such as the vmPFC, dmPFC and ACC, in BPD patients compared to NPC. They could not conclude that emotional dysregulation in BPD patients was exclusive to down-regulation.

At a p -value of 0.05 and 0.01 these studies were able with an estimated power above 80% to correctly reject the null hypothesis at a very large effect size (Table 1). For both significance levels the power was below 80% to detect a medium or large effect size.

In sum, the most consistent finding in fMRI emotion regulation studies (4 out of 5 studies) is the decreased ACC activity in BPD patients compared to NPC during down-regulation as well as during up-regulation. Results across the medial and dorsolateral prefrontal activity during both regulation conditions of negative stimuli were variable. In addition, 2 out of 3 studies indicate a difficulty to modulate the activity of the amygdala and anterior insula shown by an increased activity of these areas during down-regulation. Together conclusions concerning the support of the conceptualization of emotional dysregulation in BPD patients for negative social stimuli should be drawn with caution. The number of studies is still limited and the results seem variable across the studies. Besides, especially beyond the emotional regulatory network, there seems to be a major variation of reported brain areas and some studies even report a complete opposite pattern of brain activity compared to other studies.

5. Impulsivity in BPD

To date, three fMRI studies have examined impulsivity in BPD, they used either a go/no-go task (Jacob et al., 2013; Silbersweig et al., 2007) or an affective Stroop task (Wingenfeld et al., 2009; Table 1). The results of these studies will be discussed with respect to earlier reported brain areas involved in impulsivity. An overview of all results is given in Table 2.

Concerning both studies which used the go/no-go task, the task design and instructions differed. Silbersweig et al. (2007) used an affective go/no-go task in which participants were instructed to

press a button immediately after reading a word. The words used differed in their emotional valence and appeared in normal or italic font. Participants were instructed to inhibit their response after a word in italics. Differences in impulsivity were examined by contrasting negative no-go word trials with neutral no-go word trials (negative no-go trials). Jacob et al. (2013) used a letter-based go/no-go task in which participants had to press a button corresponding to all letters except the letter "X", after the induction of an angry, joyful or neutral mood. To examine differences in impulsivity the no-go trials after the anger induction were contrasted with the no-go trials after neutral induction (anger no-go trials). Finally, in the Stroop task by Wingenfeld et al. (2009) the participants were instructed to name the color of the presented words as fast and accurate as possible. Each color was represented by a respective colored button on a button box. In this task neutral, general negative and individual negative words were used. Brain activity during general and individual words was compared with brain activity during neutral words to examine differences in impulsivity.

The results of the go/no-go task of Silbersweig et al. (2007) showed during the negative no-go trials a greater activity in the lateral OFC, anterior insula and ACC, and less activity in the medial OFC and subgenual ACC in BPD patients, compared to NPC. Additionally, the [no-go minus go] \times [negative minus neutral] interaction showed a greater activity in the dlPFC in BPD patients compared to NPC. Jacob et al. (2013) reported in BPD patients compared to NPC, a decreased activity in the inferior frontal cortex during the anger no-go trials. The results of the Stroop task showed no significant differences between the BPD patients and NPC in brain areas associated with response inhibition during the presentation of the general negative minus the neutral trials (Wingenfeld et al., 2009). For the comparison of individual negative words a decreased ACC activity was shown in BPD patients. A different pattern of brain activity was shown between the go/no-go task and the Stroop task. The Stroop task was less associated with response inhibition related brain areas and a decreased ACC activity, while the go/no-go task was more associated with response inhibition related areas and an increased ACC activity.

At a p -value of 0.05 and 0.01 these studies had an estimated power above 80% to correctly reject the null hypothesis at a very large effect size (Table 1). For both significance levels the power was insufficient (below 80%) to correctly reject the null hypothesis at a medium or large effect size.

Taken together, conflicting results of brain areas involved in inhibition are shown by the impulsivity studies when negative emotions are evoked in BPD patients. However, the fMRI studies examining impulsivity in BPD patients comprise quite a diversity of task designs, which might explain the variety of brain areas reported across the studies. From this data it seems too early to draw conclusions concerning the hypothesis that BPD patients have difficulty in modulating their impulses in the setting of a negative state.

6. Discussion

The present review provides an overview of fMRI studies examining the neural correlates of emotional sensitivity, emotion regulation and impulsivity in BPD patients in response to negative stimuli. Regarding emotional sensitivity in BPD patients, in line with the hypothesis an enhanced activity of the amygdala was shown to be most consistent across the studies. The hypothesis that emotional dysregulation in BPD patients would be manifested from neural correlates of increased limbic areas (e.g. amygdala) and decreased regulatory areas (e.g. vlPFC, dlPFC, ACC) was partly supported. A consistent decreased activity of the ACC was shown, while the medial and dorsolateral prefrontal areas showed variable

activity. Evidence of a failure (lack of activation) of inhibitory areas (e.g. IFG, vmPFC, dlPFC, ACC) possibly underlying impulsivity in BPD patients is inconclusive. The overall findings are more inconclusive as expected, and open new avenues for future research.

First it should be noted that the studies reviewed have low statistical power, even at lenient (uncorrected) p -levels of 0.05 and 0.01, which limits the likelihood of finding a true effect. These studies could only detect very large effect sizes. The average statistical power used in different subfields of cognitive neuroimaging is already low, between 8 and 31%, and it is with the scientific developments nowadays more important to investigate subtle effects than before (Button et al., 2013). In order to increase the power and detect smaller effects one should increase the sample size. Another approach is to try to increase the effect sizes by improving the signal/noise ratio by methodological and technical means. For example, scanning parameters can be optimized to reduce signal drop out and image distortions (Weiskopf et al., 2006). Dependent on the brain area of interest, one can adjust the slice tilt, direction of the phase-encoding and z-shimming moment to optimize BOLD sensitivity. In addition, while it is assumed that there is a linear relationship between the neural activity and hemodynamic response, equal for all participants, it is well established that this relationship is not always linear and varies across participants. Therefore, nonlinear temporal statistical models might sometimes be more accurate in estimating the temporal relationship between the neural activity and hemodynamic response and could increase imaging power (Liu et al., 2001). Finally, taking into account anatomical variability, by means of refining brain normalization or performing a surface based alignment technique, could also increase statistical power (Frost and Goebel, 2012). For instance, cortex based alignment uses detailed individual curvature information to align the brains of the individual participants to a group average. In conclusion, aforementioned recommendations can be applied in order to reach the necessary increase of imaging power to detect smaller effects.

Additionally, a number of other methodological issues could explain the inconsistencies such as different implementation of emotion regulation strategies, use of medication and choice of neutral stimuli. Also different measurement and analyzing methods concerning the involvement of the amygdala. Topics to consider improving future research are manipulation of self-regulation, a more extensive range of stimuli, gender differences and the use of a clinical control group. We will now discuss these issues in more detail.

6.1. Inconsistencies concerning the involvement of the amygdala in BPD

Early studies of the amygdala revealed that the amygdala plays a critical role in the processing of fear (Whalen, 1998). Nowadays it is suggested that the amygdala plays a broader role in emotion related processes for a wide range of stimuli (e.g. negative, positive and social; Adolphs and Spezio, 2006; Phan et al., 2002). Therefore, recently more general approaches assume that the amygdala is not specifically sensitive to emotional valence of stimuli, but more associated with salience, novelty or arousal. Furthermore, the amygdala is extensively connected with cortical and subcortical structures. Because of its broad connectivity, the amygdala influences cognitive interactions in response to emotional stimuli such as emotional or reward learning, memory enhancement, attention modulation, decision making and regulation (e.g. Bechara et al., 2003; Pessoa, 2011; Phelps, 2006).

It is interesting that while the emotional dysregulation theory suggests an association with a hyperreactivity of the amygdala, some studies did not find this increased amygdala response

(Guitart-Masip et al., 2009; Koenigsberg et al., 2009b), while others showed an amygdala response after a ROI analysis or a small volume correction (Koenigsberg et al., 2009a; Schulze et al., 2011). These inconsistent findings can be explained in three-fold. First, it can be difficult to detect amygdala responses. This could be due to its localization next to air-filled spaces leading to susceptible artifacts that result in signal dropouts and image distortions (Morawetz et al., 2008). Therefore, to get more insight in the involvement of the amygdala, it would be advised to optimize scanning acquisition parameters. A recent study investigated rather simple modifications at the acquisition level to reduce susceptibility artifacts of the amygdala (Morawetz et al., 2008). It is suggested that a slice thickness of 2 mm, slice orientation along the AC–PC plane, 36 mm echo time and 4 mm spatial filter result in the least artifacts. Additionally, because of the massive corrections for multiple testing in fMRI data it is difficult to detect weak differential activation levels of the amygdala in a whole brain analysis. To reduce the multiple comparisons problem caused by the large number of voxels, ROI analyses can be performed (Poldrack, 2007). Since the response profile of the amygdala across hypothesis-relevant conditions forms an important basis of testing theories about emotional sensitivity and emotion regulation in BPD, it is suggested to perform a ROI analysis of this area (in combination with increased sample size, see above) in order to enhance detection sensitivity. This will also substantiate interpretations in case a lack of activation or a lack of group differences is found. The same argument holds for adjustment of the statistical threshold, one could consider exploring whether group differences of the amygdala are present at the most liberal p -value of 0.05 (uncorrected), to prevent type-II errors.

Second, the possibility of amygdala habituation might be present when repeatedly presenting similar emotional stimuli. Previous studies in NPC showed that the amygdala response rapidly declines after repeatedly presented facial stimuli (Breiter et al., 1996) and visual scenes (Fischer et al., 2000). The only study which showed a group difference in the amygdala after a whole brain analysis was the study of Herpertz et al. (2001). Interestingly, they measured emotional sensitivity during one single run, while other studies acquired images throughout more runs presenting stimuli repeatedly (Koenigsberg et al., 2009a,b; Niedtfeld et al., 2010; Schulze et al., 2011). This might be suggestive evidence for a habituation effect of the amygdala. Consequently it would be worthwhile to take into account this possible habituation effect by means of including time as a variable in the analysis. This is especially interesting since the theory of Linehan makes a statement about delayed habituation effects concerning emotional responses in BPD patients. It is suggested that BPD patients are characterized by a prolonged emotional experience due to a slow return to baseline arousal compared to NPC. Two recent fMRI studies showed a lack of decrease of amygdala activity with time after repeatedly presented pictures in BPD patients compared to NPC (Hazlett et al., 2012; Kamphausen et al., 2013). This delayed habituation accounted for the hyperactivity of the amygdala and could be interpreted as evidence for the prolonged duration of emotional responses in BPD patients. Of note, habituation effects could also exhibit in various other brain areas implicated in emotion processing such as the ACC, medial PFC and dlPFC (Phan et al., 2003; Wright et al., 2001). Studying habituation will help to identify a core neural network of emotional sensitivity in BPD patients.

Third, individual differences in dissociation might explain conflicting findings across the studies. BPD is associated with the presence of dissociative symptoms (American Psychiatric Association, 2013; Zanarini et al., 2000). According to the frontolimbic disconnection model of dissociation, the medial PFC inhibits the amygdala and dampens the emotional reactivity and the autonomic response (Sierra and Berrios, 1998). A study in BPD patients showed that patients with low dissociation showed a larger startle response

compared to patients with high dissociation (Ebner-Priemer et al., 2005). This suggests that the moderating effect of dissociation should be taken into account.

In sum, due to the importance of the amygdala for testing the hypothesis, scanning parameters to detect the amygdala should be optimized and (exploratory) ROI analysis or adjustment of the statistical threshold should be considered. Additionally, habituation of amygdala responses should be investigated explicitly, especially with regard to the hypothesis of a delayed habituation in BPD patients. Finally, dissociation differences should be taken into account.

6.2. Beyond the amygdala

When the emotional dysregulation theory of BPD was first proposed (Linehan, 1993) the main focus of fMRI studies was on the amygdala. However, considering the findings of the present review one might propose that the neural network involved in BPD entails more than a hyperactivity of the amygdala (Table 1). BPD patients do not only show enhanced activity in brain areas associated with emotional generation and salience (i.e. amygdala; Adolphs and Spezio, 2006; Phillips et al., 2003), but also in important other brain areas, including the anterior insula, dlPFC, ACC, PCC/precuneus and STS. Other fMRI paradigms indicate that besides affective processing the anterior insula is also involved in self-awareness and empathy (Craig, 2009; Singer et al., 2009), the PCC/precuneus in self-referential processing (Cavanna and Trimble, 2006; Vogt et al., 2006), and the STS in mentalizing (Allison et al., 2000; Saxe et al., 2004). These functions are often related to social information processing (Adolphs, 2001; Olsson and Ochsner, 2008). Besides emotional instability, BPD is also characterized by difficulties of social information processing such as interpersonal relationships, social attachment and social rejection (American Psychiatric Association, 2013; Lazarus et al., 2014; Roepke et al., 2012). Therefore responses in the anterior insula, PCC/precuneus and STS might be confounded by an underlying impairment in social information processing in BPD patients. Consequently, next to an emotional social condition it might be useful to manipulate social versus non-social contents by means of including an emotional non-social condition, such as disgust, to examine which brain activity in BPD patients can be explained by difficulties in non-social emotional information processing and which can be explained by difficulties in social emotional information processing.

6.3. Emotion regulation strategies

It is suggested that BPD patients have problems to regulate their emotional responses due to failure to activate regulatory brain areas (e.g. vlPFC, dlPFC, ACC; Krause-Utz et al., 2014). An issue to pinpoint is that across the present studies in BPD patients only cognitive reappraisal strategies were investigated and it has not been examined whether certain emotion regulation strategies might be more efficient than others for BPD patients. Schulze et al. (2011) specifically state to have used a reappraisal strategy, namely reinterpretation, however the instructions used in this study could have resulted in a combination of reinterpretation and distancing. This is an important distinction to make, as Koenigsberg et al. (2009a) suggest that distancing might be a better strategy compared to reinterpreting for BPD patients since they have particular difficulty in interpersonal social situations. Therefore, it would be important to discriminate by means of a direct comparison between both reappraisal strategies reinterpretation and distancing in BPD patients which strategy is superior. Besides, it can also be helpful to extend research beyond the current applied reappraisal strategies for regulation. Another regulation strategy of interest could be distraction. Studies in NPC show that both reappraisal as well as distraction are

successful in regulating emotional responses and in decreasing the activity of the amygdala, but a stronger reduction was shown for distraction (Kanske et al., 2011; McRae et al., 2010). This might be in line with the assumption that in distraction one should focus the attention away from the emotion content of the stimulus, while in reappraisal one should focus on the emotion content of the stimulus in order to re-evaluate the stimulus. Both strategies showed an increased activation of the prefrontal and cingulate areas for cognitive control, in reappraisal associated with emotion processing and in distraction associated with selective attention. Taken this into account distraction could, next to reappraisal, also be an effective regulation strategy for BPD patients. Unlike reappraisal and distraction, suppression occurs late in the emotions generation process (i.e. response-focused) and requires more effort to manage emotional responses. Therefore, suppression is associated with poorer psychological health and considered to be an unhealthy regulation strategy (John and Gross, 2004). It might be that BPD patients mainly use suppression as regulation strategy. However, this is difficult to examine with current regulation paradigms because BPD patients are instructed to apply reappraisal techniques. Consequently it should be examined which regulation strategy BPD patients use, and if they use suppression how this might differ from instructed regulation strategies such as reappraisal and distraction.

Additionally, research in NPC has demonstrated that with regard to timing the PFC shows an early response during cognitive reappraisal (0–4.5 s; Goldin et al., 2008). In accordance with these results, another study in BPD patients compared to NPC also showed brain activity particularly in the early interval in both groups (Lang et al., 2012). Nevertheless, in order to regulate their emotional responses BPD patients failed to activate the prefrontal brain areas (e.g. dlPFC, dmPFC, ACC) in this early phase. This suggests that optimal cognitive strategies are those that decrease limbic activity early in the emotion generation process.

Another matter to consider in future research might be the difficulty to verify how and if participants performed the regulation strategies the way they were instructed. Most of the studies relied on self-report measures, but did not include objective measures like eye-gaze to monitor performances of the participants within the scanner. Results of a study in NPC showed that during the regulation condition participants fixated shorter at the emotional parts of the image compared to the attend condition (van Reekum et al., 2007). These gaze fixations predicted changes in the blood-oxygen-level dependent (BOLD) signal change in brain areas associated with the regulation condition. So since looking away or closing their eyes could intervene with regulation responses monitoring eye-gaze is an interesting measure to control for this possible interference.

Taken together, to examine whether BPD patients differ in the neural correlates of different strategies of emotion regulation, more research should be done to, direct comparisons of various emotion regulation strategies, whilst assessing to what degree participants actually use the intended strategy. Furthermore, one should investigate which emotion regulation strategy is most effective for BPD patients.

6.4. Manipulation of self-regulation

BPD patients are often confronted with social-emotional triggers or situations in which they have difficulty regulating their emotions or inhibiting their impulsive responses. One could therefore hypothesize that the demands of the kind of studies discussed in the present review are high for BPD patients and therefore they might become exhausted. The strength model of self-regulation (limited-resources model) of Baumeister theorized that self-regulation relies upon limited resources, this is also referred to as ego depletion (Baumeister and Heatherton, 1996). It is common that people try to bring themselves out a negative

emotion, therefore we use our resources to intervene in ongoing emotions and regulate our negative emotions. In this view negative emotions might predispose attempts at self-regulation. Continuously regulating might, according to this model, result in 'depletion' of self-regulation resources. A recent study in NPC demonstrated that compared to the control group, participants who engaged in effortful self-regulation showed an increased activity of the amygdala and reduced functional connectivity between the amygdala and vmPFC for negative scenes (Wagner and Heatherton, 2013). This might indicate that after effortful self-regulation a failure in top-down control of the amygdala occurs, which could result in an increased difficulty of regulating emotions or inhibiting impulsivity.

Recently research has begun to explore countermeasures to overcome ego depletion; a novel stimulus, a change of context or new motivation can bring about a return to previous levels of functioning, questioning the limited-resources model (Martijn et al., 2006). This might suggest that a depleted state does not reflect complete exhaustion but a temporary deficit. Therefore, it could also be that the phenomena attributed to depletion in earlier studies are difficulties in maintaining sustained attention. In BPD patients this might be caused by a competition for priority of unpleasant emotions or intrusions. In the future experimental manipulation of specific self-regulation strategies in the social and/or emotional domain should be examined in BPD patients to further shed light on what self-regulation processes are compromised in BPD.

6.5. Use of psychotropic medication

Use of psychotropic medication is very common in BPD. About 75% of the BPD patients are regularly taking psychotropic medication, and these rates remain relatively stable after six years follow-up (Zanarini et al., 2004). It is assumed that different classes of psychotropic medication target specific symptoms of BPD; antidepressants and mood stabilizers are often used to target affective dysregulation and impulsive-behavioral dyscontrol, and antipsychotics for cognitive-perceptual symptoms (Lieb et al., 2004). Following these statistics, the majority of the BPD fMRI studies seem unrepresentative, as 10 out of the 15 reviewed studies excluded BPD patients currently using medication. However, research indicates that use of medication is an important confounding factor when studying brain activity. For example, it has been shown that psychotropic medication (e.g. SSRIs), compared to placebo, dampens amygdala activity in response to fearful facial expressions (Anderson et al., 2007; Arce et al., 2008; Murphy et al., 2009). Aware of these findings, many researchers are hesitant to include patients on medication and often require patients to be free of medication several weeks prior to scanning, ranging from 2 (Koenigsberg et al., 2009a,b; Niedtfeld et al., 2010; Schulze et al., 2011) till 8 weeks (Guitart-Masip et al., 2009; Lang et al., 2012). However, for some medication the washed out effect could be several months and even if the medication is washed out there still can be lasting effects in the brain such as structural, connectivity or compensatory changes (Hafeman et al., 2012). Furthermore, requiring patients to stop their medication seems ethically problematic and is likely to contribute to some form of sampling bias.

An often observed approach to the restriction of medication use, is the application of post hoc statistical analyses in which medicated versus non-medicated participants are compared to replicate the changes in brain areas in both groups. A limitation of this approach is that these analyses often lack the power to reliably assess the influences of medication on brain activity. As a solution to this problem it is suggested that researchers should examine correlations between medication load (i.e. number and dose) and changes in brain activity, which should have more

variance and there might be enough variance to add as a regressor in the analysis (Hafeman et al., 2012). Another problem with such approaches is that medication use is generally not randomized, and thus there is a considerable risk to covary out not so much possible medication effects, but other (unknown) relevant characteristics that are associated with (particular forms of) medication use.

A different approach to understanding the effect of medication on brain activity, comes from the field of pharmacological MRI (phMRI). A promising technique to get a better insight in the effect of medication on brain activity in default state and estimate medication-induced changes of brain activity, is arterial spin labeling (ASL; Wang et al., 2011). ASL allows for measuring the absolute blood flow and thus in contrast to BOLD provides a more quantitative estimate of blood perfusion. Taken into account the information of medication effect on baseline perfusion, it is able to determine the net effect of medication in the active state (Wang et al., 2011).

In sum, more insight must be gained in the effect of medication on brain activity found within the BPD population. Therefore it is important to report adequately the type and dose of medication, number of medications and even past use of medication. To control as much as possible for the effects of medication on brain activity one might add medication load as a regressor in the analysis or use the ASL approach.

6.6. How neutral is neutral?

To examine the neural correlates of the processing of emotional stimuli, in fMRI studies it is common to use a neutral stimuli as a control condition. The comparison of for example negative versus neutral scenes gives the opportunity to examine the emotional content of the pictures by itself and therefore seems to be the most elegant contrast. However, an essential, but somehow neglected, issue in BPD neuroimaging research concerns the interpretation of neutral stimuli in BPD patients. Experimental studies showed that BPD patients tend to interpret neutral facial expressions as more negative compared to NPC (Domes et al., 2008; Wagner and Linehan, 1999). The authors explain this in terms of a negativity bias, suggesting that BPD patients are hypersensitive to social cues, especially for social exclusion and abandonment, and therefore misinterpret (social) neutral stimuli. This claim is further supported by fMRI studies showing amygdala hyperreactivity to neutral faces (Donegan et al., 2003). One should note that facial expressions are a primary source of social behavior, and BPD patients are hypersensitive to interpersonal and social cues, so therefore BPD patients would more likely interpret neutral facial expressions as more negative. Additional evidence, however, is also provided by fMRI studies using IAPS pictures (Niedtfeld et al., 2010; Schulze et al., 2011). Strikingly, ROI analyses of the amygdala by Niedtfeld et al. (2010) and Schulze et al. (2011) showed that emotional reactivity was not only related to negative social scenes, but also holds for neutral social scenes. These findings suggest that BPD patients do not perceive neutral stimuli actually as neutral. This raises the question whether it is valid to ascribe neutral stimuli as a baseline measure.

For more detailed examination instead of using a simple subtraction design it is proposed to use factorial designs allowing to analyze the interaction between variables (Friston et al., 1996). Additionally, parametric designs are often used to give different levels a separate weighting. In this case the valence of each emotional picture could be rated and used as weight in the analysis of explained variance. Results from both designs are not strongly dependent on a neutral control condition as is the case for a simple two-mean (active vs. neutral) comparison.

6.7. Stimuli types

Another avenue of research is the range of emotional stimuli used in fMRI studies in BPD. This is usually restricted to negative and neutral stimuli. However, it is also important to include other stimulus categories with a different valence such as positive stimuli to examine whether in BPD patients evidence points to a general hyperreactivity to emotional stimuli or to a specificity of negative stimuli. Two studies included positive stimuli to examine emotional sensitivity in BPD patients (Arntz et al., 2015; Koenigsberg et al., 2009b). Koenigsberg et al. (2009b) did not show altered brain activity in the limbic system (e.g. amygdala) in BPD patients compared to NPC for the contrast positive minus rest. Using the contrast positive minus neutral Arntz et al. (2015) did also not find an increased brain response in the amygdala specific for BPD patients. In addition, they found weaker brain responses for the textual stimuli. Taken together, both studies do not support a generalized hypersensitivity to emotional stimuli in BPD patients.

Furthermore given that sexual abuse during childhood is often reported in BPD patients (e.g. Lobbestael et al., 2010; Zanarini et al., 2002), it is useful to examine whether stimuli with erotic content might trigger intense emotional reactions in BPD patients. Subsequently this might advocate to investigate also other BPD salient stimuli such as physical, emotional or attachment trauma, emotional experiences of abandonment or social exclusion, and anger.

6.8. Gender differences

The majority of the presently reviewed studies included solely females (7 out of 15; Table 1) or consistent predominately of females (5 out of 15; Table 1). The main reason why so few males are included is that in mental health settings BPD is more often diagnosed in females than in males, with an estimated ratio of 3:1 respectively (American Psychiatric Association, 2013; Lieb et al., 2004). Furthermore, it is expected that the inclusion of both genders will add to the observed fMRI data variability within groups, as research shows that males and females differ in emotion processing (e.g. emotional sensitivity and regulation) (Whittle et al., 2011) and impulsivity (Li et al., 2006), and that BPD symptomatology interacts with gender by inflating these differences. In line with this assumption, research indicates gender differences in the clinical presentation of BPD (Johnson et al., 2003). BPD females are more likely to display internalizing emotional behavior (e.g. feeling sad, lonely and/or anxious, social withdrawal, poor self-esteem and self-injury), compared to BPD males who engage more in externalizing, disinhibited and reactive aggressive behavior (e.g. disobeying rules, vandalism, fighting, stealing and cursing) (Johnson et al., 2003). Consequently, it seems inappropriate to investigate mixed groups without taking gender effects into account (which calls for larger samples), though only investigating females will limit the generalizability to males.

Only a few studies investigated neurobiological differences between males and females with BPD (Perez-Rodriguez et al., 2012; Soloff et al., 2003). One study showed a decreased prolactin response in BPD males compared to NPC males, which was also inversely related to impulsivity and aggression measures (Soloff et al., 2003). No differences were found between the BPD females and NPC females. These results indicated that gender differences in the serotonergic system, reflected in the prolactin response, mediate increased impulsivity in BPD males. Another study displayed gender differences in the involvement of frontal-striatal circuits in BPD patients (Perez-Rodriguez et al., 2012). Results suggested that a reduced striatal glucose metabolism in BPD males compared to BPD females and NPC is associated with difficulties in affective learning and social decision making. Together, the aforementioned

studies indicate that BPD has gender-specific symptom expressions and related neurobiological responses.

In conclusion, given the predominance of female BPD patients in mental health care samples and the effect of increasing variability of already very variable fMRI datasets when both sexes are included, the focus on female BPD patients in present fMRI studies is understandable. However, at the same time differences between male and female BPD patients in emotional sensitivity, emotion regulation and impulsivity remains understudied. Consequently, future studies should directly compare male and female BPD patients, to clarify the potential role of gender in BPD.

6.9. Importance of clinical control groups

An important issue in BPD research is the psychiatric comorbidity within BPD patients. BPD patients often show a variety of comorbid Axis I and Axis II disorders. The most common comorbidities of Axis I are major depression (MDD; 61–83%), posttraumatic stress disorder (PTSD; 36–56%), substance abuse (52–66%) and eating disorders (29–53%) (McGlashan et al., 2000; Zanarini et al., 1998a; Zimmerman and Mattia, 1999). In terms of Axis II, 14–30% of BPD patients have co-occurrence with paranoid personality disorder, and regarding the Cluster C personality disorders comorbidity rates are 43–47% avoidant, 16–51% dependent and 18–26% obsessive compulsive personality disorder (McGlashan et al., 2000; Zanarini et al., 1998b). On the one hand these comorbidities are typical in BPD; 'pure' BPD patients are rare and selecting them would result in a non-representative BPD group. On the other hand without proper clinical control groups we cannot rule out effects contributed by the comorbid disorders, which calls the BPD specificity of the findings into question. Unfortunately, sample sizes for subgroup analyses controlling for specific comorbid disorders are often too small to be valid. Therefore, future fMRI studies should include additional clinical groups as for example most common comorbidities like patients with PTSD, MDD and/or Cluster C personality disorder to examine BPD specificity.

In addition, given that traumatic experiences including various abuse and neglect are very common in BPD patients (Lobbestael et al., 2010; Zanarini et al., 2002) it might be important to take trauma into account. This would also make trauma-specific and BPD-specific comparisons possible and raises understanding to what degree trauma contributes to the neural mechanisms underlying emotional processing in BPD patients. Lang et al. (2012) did not find differences in brain activity between trauma-experienced BPD patients and trauma-experienced women, and therefore suggested that trauma experiences rather than BPD modulated emotional regulation. Both groups showed different brain activity compared to NPC.

It should be noted that results could be sensitive for a combination of certain comorbidities and symptoms in subgroups of BPD patients. As mentioned earlier BPD is often associated with PTSD, childhood trauma, and dissociation, therefore comparing BPD subgroups with these comorbidities or symptoms with clinical control groups also covering these comorbidities or symptoms is essential.

Finally, an interesting clinical control group is women with premenstrual dysphoric disorder (PMDD) or premenstrual syndrome (PMS). Symptoms of PMDD/PMS are mood swings, irritability, depressed mood, feelings of hopelessness, anxiety or tension, and impairment of interpersonal functioning (American Psychiatric Association, 2013; Grady-Weliky, 2003). Many of these affective symptoms are similar to emotional instability of BPD. Therefore, to examine BPD specificity PMDD/PMS is an informative control group. Of note, two fMRI studies in NPC showed that the menstrual

cycle modulates brain activity of the amygdala, hippocampus and OFC in response to emotional stimuli (Andreano and Cahill, 2010; Protopopescu et al., 2005). For this reason controlling for menstrual cycle might be important to take into account.

In sum, to investigate BPD specificity appropriate clinical control groups should be included in (fMRI) research designs. Moreover, it is advised to take confounding factors such as trauma and menstrual cycle into consideration.

6.10. Future directions: dimensional approach

Recently the study of basic processes that play a role in various forms of psychopathology has been promoted as a better way to gain understanding of mental disorders, than the study of categorical disorders (Cuthbert, 2014; National Institute of Mental Health, 2008). The goal of the so called Research Domain Criteria project (RDoC) is to develop new ways of classifying mental disorders based on genetics, neuroscience and behavioral science, to provide a foundation for precision diagnostics and treatment. With regard to this project, fMRI research could focus on emotional regulation problems and impulsivity in general, rather than investigate single disorders. At the moment it seems difficult to tell whether that approach will bring the field further, though there is certainly an appeal in it. One of the problems is that it is difficult to determine what the essential underlying processes are. Impulsivity, for instance, is in itself a multidimensional construct (Evenden, 1999; Moeller et al., 2001) and the impulsivity that plays a role in the type of mental health problems we currently label with BPD is not necessarily the same as in attention deficit/hyperactivity disorder (ADHD) or in antisocial PD (Moeller et al., 2001). Similarly, emotion regulation has many facets (Gross, 1998, 2007) and it is unlikely that one facet is essential for all kinds of psychopathology. Such an approach would therefore involve the development of a taxonomy of the basic processes that are relevant for different types of psychopathology. On the other hand, neuroimaging studies could play an important role in defining the essential dimensions of such constructs and help clarifying what dimension plays a role in what disorder. Consequently, this will reduce the heterogeneity, makes it easier to define and get clear insight in the research population and might have an important contribution to the possibility of finding small effects.

7. Conclusion

In conclusion, emotional sensitivity, emotion regulation and impulsivity in BPD patients are important topics in neuroimaging research today. Emotional sensitivity, emotion regulation and impulsivity problems in BPD patients can be understood in terms of an impaired inhibition from the prefrontal brain areas on the limbic areas. However, the present review shows that results across the studies appear not to be that clear as previously suggested. By all means some conclusions need to be interpreted with caution and advocate for more studies and replications of the results. Understanding underlying neurocircuits might provide important insights in BPD and might be valuable to improve therapies and ultimately personal conditions for BPD patients and societal burden. Future studies should increase the employed sample sizes to increase statistical power and examine more subtle effects. Additionally, they should focus more on BPD specificity such as the time courses of the amygdala, different regulation strategies, manipulation of self-regulation, medication use, a wider range of stimuli (e.g. positive, non-social), gender effects and the inclusion of a clinical control group.

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References

- Adolphs, R., 2001. The neurobiology of social cognition. *Curr. Opin. Neurobiol.* 11, 231–239.
- Adolphs, R., Spezio, M., 2006. Role of the amygdala in processing visual social stimuli. *Prog. Brain Res.* 156, 363–378.
- Allison, T., Puce, A., McCarthy, G., 2000. Social perception from visual cues: role of the STS region. *Trends Cogn. Sci.* 4, 267–278.
- American Psychiatric Association, 2013. *Diagnostic and Statistical Manual of Mental Disorder*, 5th ed. American Psychiatric Association, Arlington, VA.
- Anderson, I.M., Del-Ben, C.M., McKie, S., Richardson, P., Williams, S.R., Elliott, R., Deakin, J.F., 2007. Citalopram modulation of neuronal responses to aversive face emotions: a functional MRI study. *Neuroreport* 18, 1351–1355.
- Andreano, J.M., Cahill, L., 2010. Menstrual cycle modulation of medial temporal activity evoked by negative emotion. *Neuroimage* 53, 1286–1293.
- Arce, E., Simmons, A.N., Lovero, K.L., Stein, M.B., Paulus, M.P., 2008. Escitalopram effects on insula and amygdala BOLD activation during emotional processing. *Psychopharmacology (Berl.)* 196, 661–672.
- Arntz, A., Gielen, D., van der Heijden, P., Siep, N., Cima, M., van der Veen, F., 2015. Central and Peripheral Nervous System Responses to Visual and Textual Emotional Stimuli in Borderline Personality Disorder Patients: Specificity and Effects of Psychotherapy (submitted for publication).
- Baumeister, R., Heatherton, T., 1996. Self-regulation failure: an overview. *Psychol. Inq.* 7, 1–15.
- Bechara, A., Damasio, H., Damasio, A.R., 2003. Role of the amygdala in decision-making. *Ann. N. Y. Acad. Sci.* 985, 356–369.
- Bland, A.R., Williams, C.A., Scharer, K., Manning, S., 2004. Emotion processing in borderline personality disorders. *Issues Ment. Health Nurs.* 25, 655–672.
- Breiter, H.C., Etcoff, N.L., Whalen, P.J., Kennedy, W.A., Rauch, S.L., Buckner, R.L., Strauss, M.M., Hyman, S.E., Rosen, B.R., 1996. Response and habituation of the human amygdala during visual processing of facial expression. *Neuron* 17, 875–887.
- Button, K.S., Ioannidis, J.P., Mokrysz, C., Nosek, B.A., Flint, J., Robinson, E.S., Munafò, M.R., 2013. Power failure: why small sample size undermines the reliability of neuroscience. *Nat. Rev. Neurosci.* 14, 365–376.
- Carpenter, R.W., Trull, T.J., 2013. Components of emotion dysregulation in borderline personality disorder: a review. *Curr. Psychiatry Rep.* 15, 335.
- Cavanna, A.E., Trimble, M.R., 2006. The precuneus: a review of its functional anatomy and behavioural correlates. *Brain* 129, 564–583.
- Craig, A.D., 2009. How do you feel – now? The anterior insula and human awareness. *Nat. Rev. Neurosci.* 10, 59–70.
- Crowell, S.E., Beauchaine, T.P., Linehan, M.M., 2009. A biosocial developmental model of borderline personality: elaborating and extending Linehan's theory. *Psychol. Bull.* 135, 495–510.
- Cuthbert, B.N., 2014. The RDoC framework: facilitating transition from ICD/DSM to dimensional approaches that integrate neuroscience and psychopathology. *World Psychiatry* 13, 28–35.
- Davidson, R.J., Irwin, W., 1999. The functional neuroanatomy of emotion and affective style. *Trends Cogn. Sci.* 3, 11–21.
- Domes, G., Czeschnek, D., Weidler, F., Berger, C., Fast, K., Herpertz, S.C., 2008. Recognition of facial affect in borderline personality disorder. *J. Pers. Disord.* 22, 135–147.
- Domes, G., Schulze, L., Herpertz, S.C., 2009. Emotion recognition in borderline personality disorder – a review of the literature. *J. Pers. Disord.* 23, 6–19.
- Domes, G., Winter, B., Schnell, K., Vohs, K., Fast, K., Herpertz, S.C., 2006. The influence of emotions on inhibitory functioning in borderline personality disorder. *Psychol. Med.* 36, 1163–1172.
- Donegan, N.H., Sanislow, C.A., Blumberg, H.P., Fulbright, R.K., Lacadie, C., Skudlarski, P., Gore, J.C., Olson, I.R., McGlashan, T.H., Wexler, B.E., 2003. Amygdala hyperreactivity in borderline personality disorder: implications for emotional dysregulation. *Biol. Psychiatry* 54, 1284–1293.
- Ebner-Priemer, U.W., Badeck, S., Beckmann, C., Wagner, A., Feige, B., Weiss, I., Lieb, K., Bohus, M., 2005. Affective dysregulation and dissociative experience in female patients with borderline personality disorder: a startle response study. *J. Psychiatr. Res.* 39, 85–92.
- Ebner-Priemer, U.W., Welch, S.S., Grossman, P., Reisch, T., Linehan, M.M., Bohus, M., 2007. Psychophysiological ambulatory assessment of affective dysregulation in borderline personality disorder. *Psychiatry Res.* 150, 265–275.
- Ekman, P., Friesen, W.V., 1979. *Pictures of Facial Affect*. Consulting Psychologists, Palo Alto, CA.
- Evenden, J.L., 1999. Varieties of impulsivity. *Psychopharmacology (Berl.)* 146, 348–361.
- Fischer, H., Furmark, T., Wik, G., Fredrikson, M., 2000. Brain representation of habituation to repeated complex visual stimulation studied with PET. *Neuroreport* 11, 123–126.
- Friston, K.J., Price, C.J., Fletcher, P., Moore, C., Frackowiak, R.S., Dolan, R.J., 1996. The trouble with cognitive subtraction. *Neuroimage* 4, 97–104.

- Frost, M.A., Goebel, R., 2012. Measuring structural–functional correspondence: spatial variability of specialised brain regions after macro-anatomical alignment. *Neuroimage* 59, 1369–1381.
- Garavan, H., Ross, T.J., Stein, E.A., 1999. Right hemispheric dominance of inhibitory control: an event-related functional MRI study. *Proc. Natl. Acad. Sci. U.S.A.* 96, 8301–8306.
- Goldin, P.R., McRae, K., Ramel, W., Gross, J.J., 2008. The neural bases of emotion regulation: reappraisal and suppression of negative emotion. *Biol. Psychiatry* 63, 577–586.
- Goodman, M., Carpenter, D., Tang, C.Y., Goldstein, K.E., Avedon, J., Fernandez, N., Mascitelli, K.A., Blair, N.J., New, A.S., Triebwasser, J., Siever, L.J., Hazlett, E.A., 2014. Dialectical behavior therapy alters emotion regulation and amygdala activity in patients with borderline personality disorder. *J. Psychiatr. Res.* 57, 108–116.
- Grady-Weliky, T.A., 2003. Clinical practice. Premenstrual dysphoric disorder. *N. Engl. J. Med.* 348, 433–438.
- Gross, J.J., 1998. The emerging field of emotion regulation: an integrative review. *Rev. Gen. Psychol.* 2, 271–299.
- Gross, J.J., 2007. *Handbook of Emotion Regulation*. Guilford Publications, New York, NY.
- Guitart-Masip, M., Pascual, J.C., Carmona, S., Hoekzema, E., Berge, D., Perez, V., Soler, J., Soliva, J.C., Rovira, M., Bulbena, A., Vilarroya, O., 2009. Neural correlates of impaired emotion discrimination in borderline personality disorder: an fMRI study. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 33, 1537–1545.
- Hafeman, D.M., Chang, K.D., Garrett, A.S., Sanders, E.M., Phillips, M.L., 2012. Effects of medication on neuroimaging findings in bipolar disorder: an updated review. *Bipolar Disord.* 14, 375–410.
- Hazlett, E.A., Speiser, L.J., Goodman, M., Roy, M., Carrizal, M., Wynn, J.K., Williams, W.C., Romero, M., Minzenberg, M.J., Siever, L.J., New, A.S., 2007. Exaggerated affect-modulated startle during unpleasant stimuli in borderline personality disorder. *Biol. Psychiatry* 62, 250–255.
- Hazlett, E.A., Zhang, J., New, A.S., Zelmanova, Y., Goldstein, K.E., Haznedar, M.M., Meyerson, D., Goodman, M., Siever, L.J., Chu, K.W., 2012. Potentiated amygdala response to repeated emotional pictures in borderline personality disorder. *Biol. Psychiatry* 72, 448–456.
- Herpertz, S.C., Dietrich, T.M., Wenning, B., Krings, T., Erberich, S.G., Willmes, K., Thron, A., Sass, H., 2001. Evidence of abnormal amygdala functioning in borderline personality disorder: a functional MRI study. *Biol. Psychiatry* 50, 292–298.
- Herpertz, S.C., Kunert, H.J., Schwenger, U.B., Sass, H., 1999. Affective responsiveness in borderline personality disorder: a psychophysiological approach. *Am. J. Psychiatry* 156, 1550–1556.
- Horn, N.R., Dolan, M., Elliott, R., Deakin, J.F., Woodruff, P.W., 2003. Response inhibition and impulsivity: an fMRI study. *Neuropsychologia* 41, 1959–1966.
- Jacob, G.A., Gutz, L., Bader, K., Lieb, K., Tuscher, O., Stahl, C., 2010. Impulsivity in borderline personality disorder: impairment in self-report measures, but not behavioral inhibition. *Psychopathology* 43, 180–188.
- Jacob, G.A., Zvonik, K., Kamphausen, S., Sebastian, A., Maier, S., Philipsen, A., Tebartz van Elst, L., Lieb, K., Tuscher, O., 2013. Emotional modulation of motor response inhibition in women with borderline personality disorder: an fMRI study. *J. Psychiatry Neurosci.* 38, 164–172.
- John, O.P., Gross, J.J., 2004. Healthy and unhealthy emotion regulation: personality processes, individual differences, and life span development. *J. Pers.* 72, 1301–1333.
- Johnson, D.M., Shea, M.T., Yen, S., Battle, C.L., Zlotnick, C., Sanislow, C.A., Grilo, C.M., Skodol, A.E., Bender, D.S., McGlashan, T.H., Gunderson, J.G., Zanarini, M.C., 2003. Gender differences in borderline personality disorder: findings from the Collaborative Longitudinal Personality Disorders Study. *Compr. Psychiatry* 44, 284–292.
- Kamphausen, S., Schroder, P., Maier, S., Bader, K., Feige, B., Kaller, C.P., Glauche, V., Ohlendorf, S., Tebartz van Elst, L., Kloppel, S., Jacob, G.A., Silbersweig, D., Lieb, K., Tuscher, O., 2013. Medial prefrontal dysfunction and prolonged amygdala response during instructed fear processing in borderline personality disorder. *World J. Biol. Psychiatry* 14, 307–318, S301–S304.
- Kanske, P., Heissler, J., Schonfelder, S., Bongers, A., Wessa, M., 2011. How to regulate emotion? Neural networks for reappraisal and distraction. *Cereb. Cortex* 21, 1379–1388.
- Koenigsberg, H.W., Fan, J., Ochsner, K.N., Liu, X., Guise, K.G., Pizzarello, S., Dorantes, C., Guerreri, S., Tecuta, L., Goodman, M., New, A., Siever, L.J., 2009a. Neural correlates of the use of psychological distancing to regulate responses to negative social cues: a study of patients with borderline personality disorder. *Biol. Psychiatry* 66, 854–863.
- Koenigsberg, H.W., Siever, L.J., Lee, H., Pizzarello, S., New, A.S., Goodman, M., Cheng, H., Flory, J., Prohovnik, I., 2009b. Neural correlates of emotion processing in borderline personality disorder. *Psychiatry Res.* 172, 192–199.
- Krause-Utz, A., Winter, D., Niedtfeld, I., Schmahl, C., 2014. The latest neuroimaging findings in borderline personality disorder. *Curr. Psychiatry Rep.* 16, 438.
- Lang, P.J., Bradley, M.M., Cuthbert, B.N., 1997. *International Affective Picture System (IAPS): Instruction Manual and Affective Ratings*. Center of Research in Psychophysiology, University of Florida, Gainesville, FL.
- Lang, S., Kotchoubey, B., Frick, C., Spitzer, C., Grabe, H.J., Barnow, S., 2012. Cognitive reappraisal in trauma-exposed women with borderline personality disorder. *Neuroimage* 59, 1727–1734.
- Lazarus, S.A., Cheavens, J.S., Festa, F., Rosenthal, M.Z., 2014. Interpersonal functioning in borderline personality disorder: a systematic review of behavioral and laboratory-based assessments. *Clin. Psychol. Rev.* 34, 193–205.
- Leichsenring, F., Leibing, E., Kruse, J., New, A.S., Leweke, F., 2011. Borderline personality disorder. *Lancet* 377, 74–84.
- Lenzenweger, M.F., Lane, M.C., Loranger, A.W., Kessler, R.C., 2007. DSM-IV personality disorders in the National Comorbidity Survey Replication. *Biol. Psychiatry* 62, 553–564.
- Levine, D., Marziali, E., Hood, J., 1997. Emotion processing in borderline personality disorders. *J. Nerv. Ment. Dis.* 185, 240–246.
- Leyton, M., Okazawa, H., Diksic, M., Paris, J., Rosa, P., Mzengeza, S., Young, S.N., Blier, P., Benkelfat, C., 2001. Brain regional alpha-[¹¹C]methyl-L-tryptophan trapping in impulsive subjects with borderline personality disorder. *Am. J. Psychiatry* 158, 775–782.
- Li, C.S., Huang, C., Constable, R.T., Sinha, R., 2006. Gender differences in the neural correlates of response inhibition during a stop signal task. *Neuroimage* 32, 1918–1929.
- Lieb, K., Zanarini, M.C., Schmahl, C., Linehan, M.M., Bohus, M., 2004. Borderline personality disorder. *Lancet* 364, 453–461.
- Linehan, M.M., 1993. *Cognitive–Behavioral Treatment of Borderline Personality Disorder*. Guilford Press, New York.
- Liu, T.T., Frank, L.R., Wong, E.C., Buxton, R.B., 2001. Detection power, estimation efficiency, and predictability in event-related fMRI. *Neuroimage* 13, 759–773.
- Lobbetael, J., Arntz, A., 2010. Emotional, cognitive and physiological correlates of abuse-related stress in borderline and antisocial personality disorder. *Behav. Res. Ther.* 48, 116–124.
- Lobbetael, J., Arntz, A., Bernstein, D.P., 2010. Disentangling the relationship between different types of childhood maltreatment and personality disorders. *J. Pers. Disord.* 24, 285–295.
- Lynch, T.R., Rosenthal, M.Z., Kosson, D.S., Cheavens, J.S., Lejuez, C.W., Blair, R.J., 2006. Heightened sensitivity to facial expressions of emotion in borderline personality disorder. *Emotion* 6, 647–655.
- Martijn, C., Alberts, H.J.E.M., de Vries, N.K., 2006. Maintaining self-control: the role of expectancies. In: de Ridder, D.T.D., de Wit, J.B.F. (Eds.), *Self-regulation in Health Behavior*. John Wiley & Sons Ltd, Chichester, West Sussex, England, pp. 169–191.
- Mauchnik, J., Schmahl, C., 2010. The latest neuroimaging findings in borderline personality disorder. *Curr. Psychiatry Rep.* 12, 46–55.
- McGlashan, T.H., Grilo, C.M., Skodol, A.E., Gunderson, J.G., Shea, M.T., Morey, L.C., Zanarini, M.C., Stout, R.L., 2000. The Collaborative Longitudinal Personality Disorders Study: baseline axis I/II and II/II diagnostic co-occurrence. *Acta Psychiatr. Scand.* 102, 256–264.
- McRae, K., Hughes, B., Chopra, S., Gabrieli, J.D., Gross, J.J., Ochsner, K.N., 2010. The neural bases of distraction and reappraisal. *J. Cogn. Neurosci.* 22, 248–262.
- Minzenberg, M.J., Fan, J., New, A.S., Tang, C.Y., Siever, L.J., 2007. Fronto-limbic dysfunction in response to facial emotion in borderline personality disorder: an event-related fMRI study. *Psychiatry Res.* 155, 231–243.
- Moeller, F.G., Barratt, E.S., Dougherty, D.M., Schmitz, J.M., Swann, A.C., 2001. Psychiatric aspects of impulsivity. *Am. J. Psychiatry* 158, 1783–1793.
- Morawetz, C., Holz, P., Lange, C., Baudewig, J., Weniger, G., Irie, E., Dechent, P., 2008. Improved functional mapping of the human amygdala using a standard functional magnetic resonance imaging sequence with simple modifications. *Magn. Reson. Imaging* 26, 45–53.
- Mortensen, J.A., Rasmussen, I.A., Häberg, A., 2010. Trait impulsivity in female patients with borderline personality disorder and matched controls. *Acta Neuropsychiatr.* 22, 139–149.
- Murphy, S.E., Norbury, R., O'Sullivan, U., Cowen, P.J., Harmer, C.J., 2009. Effect of a single dose of citalopram on amygdala response to emotional faces. *Br. J. Psychiatry* 194, 535–540.
- Nater, U.M., Bohus, M., Abbruzzese, E., Ditzen, B., Gaab, J., Kleindienst, N., Ebner-Priemer, U., Mauchnik, J., Ehler, U., 2010. Increased psychological and attenuated cortisol and alpha-amylase responses to acute psychosocial stress in female patients with borderline personality disorder. *Psychoneuroendocrinology* 35, 1565–1572.
- National Institute of Mental Health, 2008. The National Institute of Mental Health Strategic Plan. Retrieved from <http://www.nimh.nih.gov/about/strategic-planning-reports/index.shtml>
- Niedtfeld, I., Schulz, L., Krisch, P., Herpertz, S.C., Bohus, M., Schmahl, C., 2010. Affect regulation and pain in borderline personality disorder: a possible link to the understanding of self-injury. *Biol. Psychiatry* 68, 383–391.
- Ochsner, K.N., Bunge, S.A., Gross, J.J., Gabrieli, J.D., 2002. Rethinking feelings: an fMRI study of the cognitive regulation of emotion. *J. Cogn. Neurosci.* 14, 1215–1229.
- Ochsner, K.N., Silvers, J.A., Buhle, J.T., 2012. Functional imaging studies of emotion regulation: a synthetic review and evolving model of the cognitive control of emotion. *Ann. N. Y. Acad. Sci.* 1251, E1–E24.
- Olsson, A., Ochsner, K.N., 2008. The role of social cognition in emotion. *Trends Cogn. Sci.* 12, 65–71.
- Perez-Rodriguez, M.M., Hazlett, E.A., Rich, E.L., Ripoll, L.H., Weiner, D.M., Spence, N., Goodman, M., Koenigsberg, H.W., Siever, L.J., New, A.S., 2012. Striatal activity in borderline personality disorder with comorbid intermittent explosive disorder: sex differences. *J. Psychiatr. Res.* 46, 797–804.
- Pessoa, L., 2011. Reprint of: Emotion and cognition and the amygdala: from “what is it?” to “what’s to be done?” *Neuropsychologia* 49, 681–694.
- Phan, K.L., Fitzgerald, D.A., Nathan, P.J., Moore, G.J., Uhde, T.W., Tancer, M.E., 2005. Neural substrates for voluntary suppression of negative affect: a functional magnetic resonance imaging study. *Biol. Psychiatry* 57, 210–219.
- Phan, K.L., Liberzon, I., Welsh, R.C., Britton, J.C., Taylor, S.F., 2003. Habituation of rostral anterior cingulate cortex to repeated emotionally salient pictures. *Neuropsychopharmacology* 28, 1344–1350.
- Phan, K.L., Wager, T., Taylor, S.F., Liberzon, I., 2002. Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. *Neuroimage* 16, 331–348.

- Phelps, E.A., 2006. Emotion and cognition: insights from studies of the human amygdala. *Annu. Rev. Psychol.* 57, 27–53.
- Phillips, M.L., Drevets, W.C., Rauch, S.L., Lane, R., 2003. Neurobiology of emotion perception I: the neural basis of normal emotion perception. *Biol. Psychiatry* 54, 504–514.
- Poldrack, R.A., 2007. Region of interest analysis for fMRI. *Soc. Cogn. Affect Neurosci.* 2, 67–70.
- Protopopescu, X., Pan, H., Altemus, M., Tuescher, O., Polanecsky, M., McEwen, B., Silbersweig, D., Stern, E., 2005. Orbitofrontal cortex activity related to emotional processing changes across the menstrual cycle. *Proc. Natl. Acad. Sci. U.S.A.* 102, 16060–16065.
- Rentrop, M., Backenstrass, M., Jaentsch, B., Kaiser, S., Roth, A., Unger, J., Weisbrod, M., Renneberg, B., 2008. Response inhibition in borderline personality disorder: performance in a Go/Nogo task. *Psychopathology* 41, 50–57.
- Roepke, S., Vater, A., Preissler, S., Heekeren, H.R., Dziobek, I., 2012. Social cognition in borderline personality disorder. *Front. Neurosci.* 6, 195.
- Rosenthal, M.Z., Gratz, K.L., Kosson, D.S., Cheavens, J.S., Lejuez, C.W., Lynch, T.R., 2008. Borderline personality disorder and emotional responding: a review of the research literature. *Clin. Psychol. Rev.* 28, 75–91.
- Saxe, R., Xiao, D.K., Kovacs, G., Perrett, D.I., Kanwisher, N., 2004. A region of right posterior superior temporal sulcus responds to observed intentional actions. *Neuropsychologia* 42, 1435–1446.
- Schmahl, C.G., Elzinga, B.M., Vermetten, E., Sanislow, C., McGlashan, T.H., Bremner, J.D., 2003. Neural correlates of memories of abandonment in women with and without borderline personality disorder. *Biol. Psychiatry* 54, 142–151.
- Schmahl, C.G., Vermetten, E., Elzinga, B.M., Bremner, J.D., 2004. A positron emission tomography study of memories of childhood abuse in borderline personality disorder. *Biol. Psychiatry* 55, 759–765.
- Schnell, K., Herpertz, S.C., 2007. Effects of dialectic-behavioral-therapy on the neural correlates of affective hyperarousal in borderline personality disorder. *J. Psychiatr. Res.* 41, 837–847.
- Schulze, L., Domes, G., Kruger, 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. *Biol. Psychiatry* 69, 564–573.
- Sebastian, A., Jacob, G., Lieb, K., Tuscher, O., 2013a. Impulsivity in borderline personality disorder: a matter of disturbed impulse control or a facet of emotional dysregulation? *Curr. Psychiatry Rep.* 15, 339.
- Sebastian, A., Pohl, M.F., Kloppel, S., Feige, B., Lange, T., Stahl, C., Voss, A., Klauer, K.C., Lieb, K., Tuscher, O., 2013b. Disentangling common and specific neural subprocesses of response inhibition. *Neuroimage* 64, 601–615.
- Sierra, M., Berrios, G.E., 1998. Depersonalization: neurobiological perspectives. *Biol. Psychiatry* 44, 898–908.
- Silbersweig, D., Clarkin, J.F., Goldstein, M., Kernberg, O.F., Tuescher, O., Levy, K.N., Brendel, G., Pan, H., Beutel, M., Pavony, M.T., Epstein, J., Lenzenweger, M.F., Thomas, K.M., Posner, M.I., Stern, E., 2007. Failure of frontolimbic inhibitory function in the context of negative emotion in borderline personality disorder. *Am. J. Psychiatry* 164, 1832–1841.
- Singer, T., Critchley, H.D., Preuschoff, K., 2009. A common role of insula in feelings, empathy and uncertainty. *Trends Cogn. Sci.* 13, 334–340.
- Soloff, P.H., Kelly, T.M., Strotmeyer, S.J., Malone, K.M., Mann, J.J., 2003. Impulsivity, gender, and response to fenfluramine challenge in borderline personality disorder. *Psychiatry Res.* 119, 11–24.
- Trull, T.J., Jahng, S., Tomko, R.L., Wood, P.K., Sher, K.J., 2010. Revised NESARC personality disorder diagnoses: gender, prevalence, and comorbidity with substance dependence disorders. *J. Pers. Disord.* 24, 412–426.
- van Asselt, A.D., Dirksen, C.D., Arntz, A., Severens, J.L., 2007. The cost of borderline personality disorder: societal cost of illness in BPD-patients. *Eur. Psychiatry* 22, 354–361.
- van Reekum, C.M., Johnstone, T., Urry, H.L., Thurow, M.E., Schaefer, H.S., Alexander, A.L., Davidson, R.J., 2007. Gaze fixations predict brain activation during the voluntary regulation of picture-induced negative affect. *Neuroimage* 36, 1041–1055.
- Vogt, B.A., Vogt, L., Laureys, S., 2006. Cytology and functionally correlated circuits of human posterior cingulate areas. *Neuroimage* 29, 452–466.
- Vollm, B., Richardson, P., Stirling, J., Elliott, R., Dolan, M., Chaudhry, I., Del Ben, C., McKie, S., Anderson, I., Deakin, B., 2004. Neurobiological substrates of antisocial and borderline personality disorder: preliminary results of a functional fMRI study. *Crim. Behav. Ment. Health* 14, 39–54.
- Wagner, A.W., Linehan, M.M., 1999. Facial expression recognition ability among women with borderline personality disorder: implications for emotion regulation. *J. Pers. Disord.* 13, 329–344.
- Wagner, D.D., Heatherton, T.F., 2013. Self-regulatory depletion increases emotional reactivity in the amygdala. *Soc. Cogn. Affect. Neurosci.* 8, 410–417.
- Wang, D.J., Chen, Y., Fernandez-Seara, M.A., Detre, J.A., 2011. Potentials and challenges for arterial spin labeling in pharmacological magnetic resonance imaging. *J. Pharmacol. Exp. Ther.* 337, 359–366.
- Weiskopf, N., Hutton, C., Josephs, O., Deichmann, R., 2006. Optimal EPI parameters for reduction of susceptibility-induced BOLD sensitivity losses: a whole-brain analysis at 3T and 1.5T. *Neuroimage* 33, 493–504.
- Whalen, P.J., 1998. Fear, vigilance, and ambiguity: initial neuroimaging studies of the human amygdala. *Curr. Dir. Psychol. Sci.* 7, 177–188.
- Whittle, S., Yucel, M., Yap, M.B., Allen, N.B., 2011. Sex differences in the neural correlates of emotion: evidence from neuroimaging. *Biol. Psychol.* 87, 319–333.
- Wingenfeld, K., Rullkoetter, N., Mensebach, C., Beblo, T., Mertens, M., Kreisel, S., Toepfer, M., Driessen, M., Woermann, F.G., 2009. Neural correlates of the individual emotional stroop in borderline personality disorder. *Psychoneuroendocrinology* 34, 571–586.
- Wright, C.I., Fischer, H., Whalen, P.J., McNerney, S.C., Shin, L.M., Rauch, S.L., 2001. Differential prefrontal cortex and amygdala habituation to repeatedly presented emotional stimuli. *Neuroreport* 12, 379–383.
- Zanarini, M.C., Frankenburg, F.R., Dubo, E.D., Sichel, A.E., Trikha, A., Levin, A., Reynolds, V., 1998a. Axis I comorbidity of borderline personality disorder. *Am. J. Psychiatry* 155, 1733–1739.
- Zanarini, M.C., Frankenburg, F.R., Dubo, E.D., Sichel, A.E., Trikha, A., Levin, A., Reynolds, V., 1998b. Axis II comorbidity of borderline personality disorder. *Compr. Psychiatry* 39, 296–302.
- Zanarini, M.C., Frankenburg, F.R., Hennen, J., Silk, K.R., 2004. Mental health service utilization by borderline personality disorder patients and axis II comparison subjects followed prospectively for 6 years. *J. Clin. Psychiatry* 65, 28–36.
- Zanarini, M.C., Ruser, T., Frankenburg, F.R., Hennen, J., 2000. The dissociative experiences of borderline patients. *Compr. Psychiatry* 41, 223–227.
- Zanarini, M.C., Yong, L., Frankenburg, F.R., Hennen, J., Reich, D.B., Marino, M.F., Vujanovic, A.A., 2002. Severity of reported childhood sexual abuse and its relationship to severity of borderline psychopathology and psychosocial impairment among borderline inpatients. *J. Nerv. Ment. Dis.* 190, 381–387.
- Zimmerman, M., Mattia, J.I., 1999. Axis I diagnostic comorbidity and borderline personality disorder. *Compr. Psychiatry* 40, 245–252.