Archival Report

Biological Psychiatry

Neural Correlates of Disturbed Emotion Processing in Borderline Personality Disorder: A Multimodal Meta-Analysis

Lars Schulze, Christian Schmahl, and Inga Niedtfeld

ABSTRACT

BACKGROUND: Disturbances in the processing and regulation of emotions are core symptoms of borderline personality disorder (BPD). To further elucidate neural underpinnings of BPD, the present meta-analysis summarizes functional neuroimaging findings of emotion processing tasks, as well as structural neuroimaging findings, and investigates multimodally affected brain regions.

METHODS: Combined coordinate- and image-based meta-analyses were calculated using anisotropic effect size signed differential mapping. Nineteen functional neuroimaging studies investigating the processing of negative compared with neutral stimuli in a total of 281 patients with BPD and 293 healthy control subjects (HC) were included. In addition, 10 studies investigating gray matter abnormalities in 263 patients with BPD and 278 HC were analyzed.

RESULTS: Compared with HC, BPD patients showed relatively increased activation of the left amygdala and posterior cingulate cortex, along with blunted responses of the bilateral dorsolateral prefrontal cortex, during the processing of negative emotional stimuli. The multimodal analysis identified the left amygdala to be characterized by a combination of functional hyperactivity and smaller gray matter volume compared with HC. Hyperresponsivity of the amygdala was moderated by medication status of the patient samples. Medication-free samples were characterized by limbic hyperactivity, whereas no such group differences were found in patients currently taking psychotropic medication.

CONCLUSIONS: Results strengthen the assumption that dysfunctional dorsolateral prefrontal and limbic brain regions are a hallmark feature of BPD and therefore are consistent with the conceptualization of BPD as an emotion dysregulation disorder.

Keywords: Borderline personality disorder, Emotion, Functional magnetic resonance imaging, Meta-analysis, Signed differential mapping, Voxel-based morphometry

http://dx.doi.org/10.1016/j.biopsych.2015.03.027

Affective instability, dissociation, impulsive aggression, and nonsuicidal self-injury are the most prominent symptoms of borderline personality disorder (BPD), resulting in profound impairment of psychosocial functioning (1,2). Pivotal to the understanding of BPD are abnormalities in the processing and regulation of emotions, which contribute to most of the clinical symptoms (3–5).

Accordingly, functional neuroimaging studies in BPD have focused primarily on the processing and regulation of (negative) emotions. In response to negative stimuli, a number of studies found heightened activation of the amygdala in patients with BPD compared with healthy control subjects (HC) (6–15). However, some studies utilizing emotion processing paradigms failed to observe group differences in limbic functioning (16,17) or even support a hypoactivation of the amygdala in BPD (18,19). In addition to amygdala abnormalities, some studies observed a hyperreactivity of medial and posterior parts of the insular cortex in BPD (8,9,13,20). Albeit with considerable spatial heterogeneity, relatively reduced activations compared with HC were observed in the anterior cingulate cortex (ACC) and prefrontal structures, such as the dorsolateral prefrontal cortex (dlPFC), medial or orbitofrontal regions (8,10,18,21,22). Taken together, neuroimaging studies suggest that dysfunctional frontolimbic brain regions underlie the "emotional turmoil" in patients with BPD (23). To further advance the neuroanatomical basis of disturbed emotion processing in BPD, the present study utilized a coordinate- and image-based meta-analytic approach to summarize available neuroimaging findings.

A recent meta-analysis including between-group contrasts of 10 studies concluded that BPD is characterized by a hypoactivation of the right amygdala in response to negative compared with neutral stimuli (24). Relatively reduced activations were also found in the ACC and dlPFC, while enhanced activations were observed in the insula and posterior cingulate cortex (PCC). The authors acknowledge that results of the original studies are heterogeneous. Limbic abnormalities, for instance, might be moderated by medication status of patient

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ISSN: 0006-3223

samples, as recent studies point to beneficial effects of pharmacotherapy on symptoms of affective instability in BPD (25). Age might be an additional moderating factor of brain activation during emotion processing (26). Accordingly, the present meta-analysis investigated heterogeneity and robustness of brain abnormalities in BPD, followed by an assessment of the potential moderating effects of age and medication status on functional brain activations. To increase the sensitivity of the meta-analysis, statistical parametric maps (SPM) from original studies were included (27,28).

In addition, several studies investigated structural properties of the brain in BPD. The majority of these studies used manual tracing methods and restricted their analyses to a few selected regions of interest. These studies found smaller gray matter volume (GMV) in the bilateral amygdala and hippocampus of patients with BPD in comparison with HC (29,30). The advent of voxel-based morphometry (VBM) introduced automated segmentation procedures allowing comparison of whole-brain images without a-priori restriction to certain brain regions. VBM studies provided additional evidence for gray matter abnormalities in the ACC, dlPFC, and the orbitofrontal cortex of patients with BPD (31–34). Moreover, it stands to reason that functional and structural brain abnormalities are related, but the exact nature of this association in BPD is currently unclear. To provide initial evidence regarding multimodally affected brain regions, we calculated an additional meta-analysis of whole-brain structural abnormalities in BPD and summarized abnormalities in the functional and structural domain in a single meta-analytic map.

Consequently, the primary aims of this study are 1) to quantitatively characterize neural abnormalities in the processing of negative emotional stimuli in patients with BPD, 2) to update meta-analyses on structural brain abnormalities in BPD by using a whole-brain approach, and 3) to localize multimodally affected brain regions. Furthermore, we assessed the robustness of brain abnormalities and explored the effects of medication status and age on brain function and structure in BPD.

METHODS AND MATERIALS

Inclusion of Functional Magnetic Resonance Imaging Studies

Study Selection. Studies were identified through a literature search of articles published between 2001 (first neuroimaging study on negative emotion processing in BPD) and June 2014 using the PubMed and Web of Science databases. Keywords used were borderline personality disorder and emotion, valence, or affect and neuroimaging, or fMRI. Reference sections and citations of the articles were cross-checked to identify further articles. Studies were included if 1) patients met diagnostic criteria for BPD according to the DSM (third edition or later); 2) BPD patients were compared with a sample of HC; 3) participants completed a paradigm that included a negatively valenced emotion condition in comparison with a neutral condition (and not only, for instance, in comparison with a resting or fixation cross condition); 4) negative minus neutral contrasts for within-group and/or between-group comparisons were reported or results could be obtained from the authors; and 5) whole-brain results with stereotactic coordinates were reported/provided by the authors. To ascertain a level of homogeneity, we excluded studies of decision making (35,36), pain processing (37,38), or social rejection (39). Two studies reported on the same patient data (17,20). The follow-up study was excluded from the meta-analysis (20). Corresponding authors were contacted in case the manuscript did not explicitly report results of relevant contrasts or solely reported region-of-interest analyses. These authors were asked for further information on the outcome of relevant whole-brain contrasts, if possible by sending the original SPMs.

Nineteen studies met inclusion criteria investigating 281 patients with BPD and 293 HC (6,9–11,13,14,16–19,21,22,40–46). Sixteen studies contributed within-group comparisons (i.e., negative > neutral in BPD and/or HC) and 18 studies contributed between-group comparisons of the negative minus neutral contrast (i.e., negative > neutral in BPD > HC and vice versa). For a complete overview of study selection steps, see Figure S1 in Supplement 1. Seven studies investigated samples (partly) receiving psychotropic medication, whereas 12 studies investigated samples unmedicated at the time of investigation (unmedicated patients = 206, medicated patients = 75). For further characteristics, see Table S1 in Supplement 1.

Contrast Selection. The present meta-analysis focused particularly on the processing of negatively valenced conditions in comparison with a neutral baseline condition. For a detailed description of experimental paradigms and contrasts included, see Table S2 in Supplement 1. Whole-brain results of negative > neutral contrasts for within-group as well as between-group comparisons were included in the analysis. In case more than one negative > neutral contrast was reported in the original study (e.g., fearful, disgusted, and angry facial expressions in comparison with a neutral baseline condition), authors were asked for a combined contrast. Otherwise, activation foci of the reported contrasts were taken together and used as a single contrast to ensure that the impact of each study was independent of the number of reported contrasts. This was relevant for two studies (16,46).[1]

Inclusion of VBM Studies

Study Selection. Studies were identified through a literature search of articles published between 2003 (first whole-brain study on GMV in BPD) and June 2014 using the PubMed and Web of Science databases. Keywords used were borderline personality disorder and morphometry, voxel-based, gray matter, or voxelwise. Reference sections and citations of the articles were cross-checked. Studies were included if 1) patients met diagnostic criteria for BPD according to the DSM (third edition or later); 2) patients with BPD were compared with a sample of HC; 3) gray matter volume was analyzed; and 4) whole-brain results with stereotactic coordinates were reported. Studies reporting analyses of cortical thickness (47) or solely of regions of interest/small volumes

[1]Main findings of the functional magnetic resonance imaging meta-analysis remained stable after exclusion of both studies.

were excluded from the analysis. For a complete overview of study selection steps, see Figure S2 in Supplement 1.

Ten studies met inclusion criteria investigating 263 patients with BPD and 278 HC (31,32,34,48–54). Five studies investigated samples (partly) receiving psychotropic medication, whereas five studies investigated samples without any medication at the time of investigation (unmedicated patients = 191, medicated patients = 72). For further characteristics, see Table S3 in Supplement 1.

Statistical Analyses

The Anisotropic Effect Size Signed Differential Mapping software (AES-SDM) v4.13 (27,55,56) was used to calculate a combined coordinate and image-based meta-analysis of functional and structural brain abnormalities in BPD. AES-SDM takes the different effect sizes reported in the original studies into account. SPMs were included to increase the sensitivity of the analyses (27).

These steps were followed for coordinate-based results: coordinates and effect sizes (t or z values) were extracted from whole-brain results. In case an effect size was not reported, the significance level of a study was taken as a minimum effect size. Findings from more liberally thresholded brain regions were not taken into account. Coordinates reported in Talairach space were converted into Montreal Neurological Institute space by means of Lancaster transformation (57). Effect size information was converted to Hedges effect size. To optimize the recreation of the study maps, an anisotropic Gaussian kernel was used, which assigns higher effect sizes to voxels more correlated with peaks (56). Image- and coordinate-based study maps were used to calculate a random effects model taking into account sample size as well as intra- and between-study variance. Statistical significance was determined using standard randomization tests (50 randomizations).

Main Analyses. Within the functional magnetic resonance imaging meta-analysis, we analyzed between-group comparisons of the contrast negative > neutral for BPD > HC and for HC > BPD. Then, a meta-analysis was performed to analyze GMV differences between patients with BPD and HC. Only abnormalities that survived standard thresholding with a signed differential mapping (SDM) Z value of 1, a voxel-level (height) threshold of $p < .005$, and a cluster-level (extent) threshold of $k \geq 20$ voxels are reported (27).

Next, between-study variance was analyzed to assess significant heterogeneity of brain abnormalities. Additionally, robustness of main findings was estimated via jackknife analyses. In the jackknife analysis, the analysis is systematically repeated as many times as the number of contrasts included, while each time one contrast is discarded from the analysis. Brain regions that remain significant in all of the study combinations likely have a high degree of replicability and are therefore described as robust in the results section.

To localize brain regions with both structural and functional abnormalities in BPD, between-group contrasts of brain structure and function were summarized in a single meta-analytic map (58). The overlap of structural and functional p values was computed to identify multimodally affected brain regions. The method implemented in AES-SDM accounts for the presence of noise in the estimation of p values (58). The voxel-level threshold was decreased to $p < .0025$, as there were four tails.

Brain maps of the main analyses are available at http://neurovault.org/collections/TDPEZUJL.

Additional Analyses. Within-group effects of the contrast negative > neutral for patients with BPD and HC were used to calculate a global meta-analysis of brain regions involved in the processing of negative emotions in both groups as well as a subsequent comparison between patients with BPD and HC (cf. Supplement 1). Restricting these analyses to voxels with increased activations helped to further disentangle possible interpretations of the emotion by group interactions, which included deactivations as well. The reverse within-group contrast of neutral > negative was too rarely reported to be further analyzed.

The mean age of the patient samples as well as the medication status (overall percentage of patients receiving psychotropic medication) were used as regressors in exploratory meta-regression analyses. The voxel-level threshold was decreased to $p < .0005$ to minimize the detection of spurious relationships (59). Abnormalities were required to be present both in the slope and in one of the extremes of the regressor. Findings in regions other than those detected in the main analyses were discarded.

RESULTS

Meta-Analysis of Functional Brain Abnormalities in BPD

In comparison with HC, patients with BPD showed enhanced activity in a cluster comprising the left amygdala and the left hippocampus, as well as in clusters in the posterior cingulate gyrus and the left middle temporal gyrus (Figure 1). However, findings in the left amygdala/hippocampus region showed significant heterogeneity. Enhanced activations were also found in the left posterior insula and right superior temporal gyrus, but these findings were less robust (cf. Table 1).

Decreased activity in BPD compared with HC was observed in bilateral parts of the dlPFC and the left lingual gyrus, as well as the left superior parietal gyrus (Table 1).

Meta-regression analyses showed current medication status to modulate functional activity only in a cluster comprising the left amygdala and hippocampus (slope: [−22, 0, −26], SDM-Z = −2.68, $p = .000049$, k = 127). Medication-free samples showed enhanced activation of the amygdalar/hippocampal region in comparison with HC (0: [−18, −4, −24], SDM-Z = 3.03, $p = .00002$, k = 98), whereas no such effect was present in samples treated with psychotropic medication. Age was related to hypoactivation of the left pars triangular of the inferior frontal gyrus (slope: [−42, 18, 24], SDM-Z = −2.81, $p = .00003$, k = 124) as functional abnormalities were particularly present in older samples (1: [−42, 18, 24], SDM-Z = −2.98, $p = .00002$, k = 1015).

Meta-Analysis of Structural Brain Abnormalities in BPD

Smaller GMV in BPD was found in the right hippocampus, a large cluster comprising the pars opercularis and triangularis

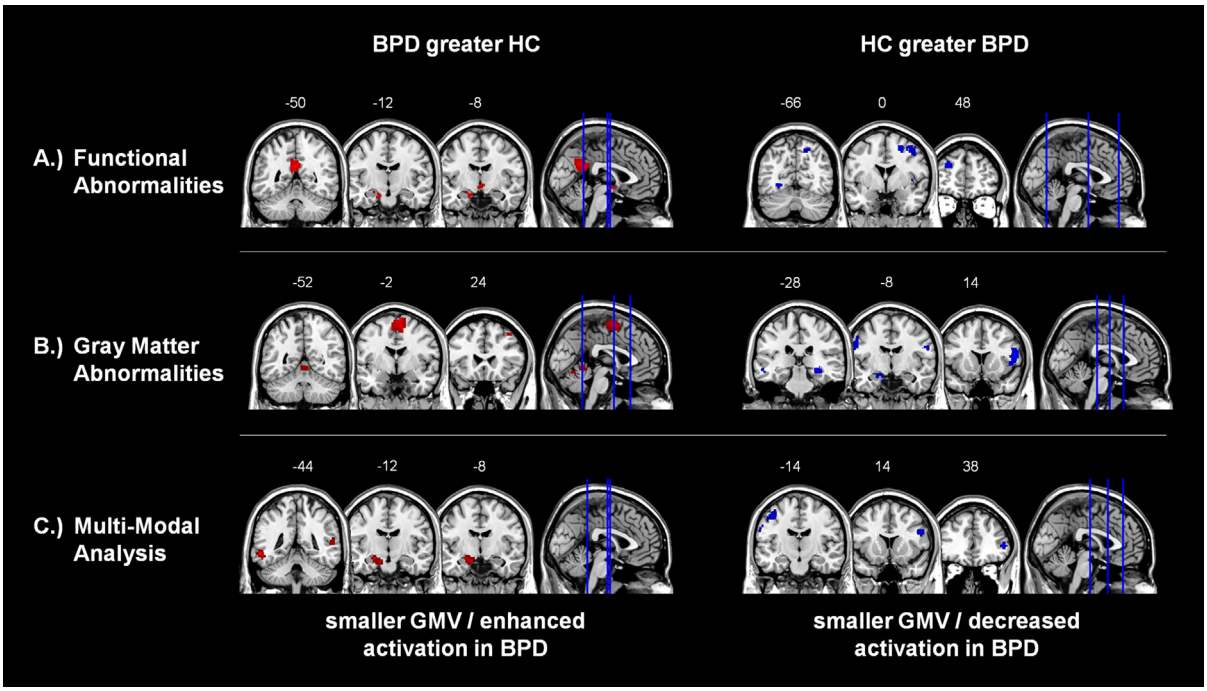

Figure 1. Visualization of the reported group differences in **(A)** emotion processing and **(B)** gray matter. Enhanced activations or greater gray matter volume (GMV) in borderline personality disorder (BPD) patients compared with healthy control subjects (HC) are presented in red, whereas decreased activation or smaller gray matter volume are presented in blue. Finally, **(C)** overlapping structural and functional abnormalities in BPD are presented. Results are overlaid on a template provided by MRIcron and the statistical threshold was set at $p < .005$ and $k > 20$ for group comparisons. Results of the multimodal analysis are thresholded at $p < .0025$ and $k > 20$ (cf. Methods and Materials).

of the right inferior frontal gyrus, as well as in parts of the bilateral temporal gyri. Less robust abnormalities were observed in the left hippocampus, the left precentral gyrus, and the right superior frontal gyrus (Figure 1). In addition, patients with BPD showed relatively greater GMV than HC in the right cerebellum and supplementary motor area, as well as in the left rolandic operculum and the right middle frontal gyrus (Table 2).

Meta-regression analyses revealed that medication status moderates GMV abnormalities in the right pars triangularis of the inferior frontal gyrus (slope: [48, 28, 2], SDM-Z = 2.21, p = .000013, k = 317). Smaller GMV in this brain region was restricted to unmedicated samples of BPD patients (0: [48, 28, 2], SDM-Z = −3.81, p = .000013, k = 353). At a trend level, age was observed to moderate GMV abnormalities of BPD patients in a cluster comprising the right amygdala and hippocampus (slope: [24, 0, −10], SDM-Z = −2.19, p = .00085, k = 167; 1: [38, −26, −14], SDM-Z = −2.94, p = .00032, k = 372) with smaller GMV being more evident in older BPD samples.

Multimodal Analysis of Functional and Structural Abnormalities in BPD

Several brain regions were identified to be affected by both structural and functional abnormalities in patients with BPD. Specifically, smaller GMV in a cluster comprising the left amygdala and hippocampus overlapped with enhanced activations during the processing of negative emotions.

In contrast, the right inferior frontal gyrus was characterized by smaller GMV and decreased activations during emotion processing. For a detailed overview of multimodally affected brain regions, see Table 3.

DISCUSSION

The present meta-analysis supports the assumption that structural and functional frontolimbic abnormalities represent a hallmark feature of BPD. In particular, our results demonstrate enhanced activation of the left amygdala along with attenuated activations of the bilateral dlPFC during the processing of negative emotional stimuli in BPD compared with healthy control subjects. Functional differences in frontolimbic brain regions were additionally found to overlap with structural differences in GMV in BPD. For instance, the multimodal analysis identified the left amygdala to be characterized by a combination of functional hyperactivity in response to negative emotional stimuli, as well as smaller GMV compared with HC. Moreover, age and current medication status of the patient samples were partly correlated with functional and structural brain abnormalities in BPD. In the following, results will be discussed by modality.

Functional Brain Abnormalities in BPD

First and foremost, our results reveal hyperactivity of the left amygdala along with blunted responses of the bilateral dlPFC during the processing of negative emotions in patients with BPD compared with HC. Abnormal functioning of these brain

Table 1. Brain Regions Exhibiting Abnormal Activation During Emotion Processing in Patients With BPD Compared With HC

	Peak		Cluster		Robustness	
Regions	MNI	SDM-Z	Size	BAs	Heterogeneity	Jackknife
Contrast: BPD > HC (Hyperactivation in BPD)						
Left posterior cingulate gyrus	−2, −50, 24	2.31	642	23, 30	ns	18/18
Left middle temporal gyrus	−58, −46, −6	2.18	49	21	ns	18/18
Left middle frontal gyrus	−28, 26, 32	2.10	21	9	ns	15/18
Left amygdala, left hippocampus	−16, −12, −22	2.09	89	28, 34, 35	Significant	18/18
Left angular gyrus	−48, −68, 42	2.08	40	39	ns	15/18
Undefined	−6, −6, −8	1.99	87	25	ns	17/18
Left insula	−32, 6, 8	1.92	24	48	ns	13/18
Right superior temporal gyrus	58, −32, 12	1.83	48	22, 42	ns	15/18
Contrast: HC > BPD (Hypoactivation in BPD)						
Left middle frontal gyrus; parts of the dorsolateral prefrontal gyrus	−24, 48, 28	−2.56	91	46	ns	18/18
Right superior frontal gyrus, parts of the dorsolateral and medial prefrontal cortex	22, 0, 54	−2.38	447	6, 8, 9	ns	18/18
Left lingual gyrus	−28, −66, −4	−2.38	111	19	ns	18/18
Left postcentral gyrus	−62, −14, 32	−2.32	244	3, 4, 6, 43, 48	ns	17/18
Left inferior frontal gyrus, pars triangularis	−50, 20, 24	−2.29	124	44, 48	ns	17/18
Right fusiform gyrus	40, −18, −22	−2.18	22	20	ns	16/18
Left superior parietal gyrus	−20, −56, 54	−2.12	58	5	ns	18/18
External capsule	34, −4, −4	−1.92	27	48	ns	14/18
Right superior parietal gyrus	22, −62, 54	−1.89	86	7	ns	16/18
Right middle frontal gyrus	32, 38, 24	−1.89	29	46	ns	17/18
Left precentral gyrus	−36, −4, 48	−1.85	34	6	ns	15/18

Results are based on contrasts of between-group comparisons.

BA, Brodmann area; BPD, borderline personality disorder; HC, healthy control subjects; MNI, Montreal Neurological Institute; ns, nonsignificant; SDM-Z, signed differential mapping Z-value.

Table 2. Brain Regions Exhibiting Abnormal Gray Matter Volume in Patients With BPD

	Peak		Cluster		Robustness	
Regions	MNI	SDM-Z	Size	BAs	Heterogeneity	Jackknife
Contrast: BPD > HC (higher GM volume in BPD)						
Right supplementary motor area	4, −2, 70	2.21	946	6	ns	10/10
Right cerebellum, lobule IV / V	0, −52, −4	1.50	181	18	ns	9/10
Right middle frontal gyrus, parts of the dorsolateral prefrontal cortex	40, 24, 50	1.42	89	9	ns	9/10
Left rolandic operculum	−42, −18, 18	1.30	20	48	ns	8/10
Contrast: HC > BPD (smaller GM volume in BPD)						
Left middle temporal gyrus	−66, −34, −8	−3.30	656	20, 21, 37	ns	10/10
Right inferior frontal gyrus, pars opercularis	54, 14, 10	−3.27	1124	4, 44, 45, 47, 48	ns	10/10
Right hippocampus	30, −28, −10	−3.24	263	20, 37	ns	10/10
Right middle temporal gyrus	54, −58, 12	−3.03	917	21, 22, 37, 42	ns	10/10
Left superior occipital gyrus	−12, −94, 10	−2.76	78	17, 18	ns	9/10
Right superior frontal gyrus, medial orbital	4, 40, −10	−2.58	123	10, 11	ns	7/10
Left hippocampus	−20, −10, −18	−2.55	86	20, 28, 30, 35	ns	7/10
Left precentral gyrus	−56, −8, 32	−2.52	84	3, 4, 6	ns	7/10
Left caudate nucleus	−10, 0, 12	−2.51	23		ns	7/10
Right paracentral lobule	4, −44, 64	−2.46	37	5	ns	8/10
Right middle temporal gyrus	52, −16, −16	−2.44	25	20	ns	8/10

BA, Brodmann area; BPD, borderline personality disorder; GM, gray matter; HC, healthy control subjects; MNI, Montreal Neurological Institute; ns, nonsignificant; SDM-Z, signed differential mapping Z-value.

Table 3. Multimodally Affected Brain Regions in Patients With BPD

	Peak		Cluster	
Regions	MNI	d	Size	BAs
Smaller GMV and Enhanced Activation in BPD				
Left middle temporal gyrus	−58, −44, −8	1.12	354	20, 21, 22, 37
Left amygdala, left hippocampus	−12, −12, −22	.93	356	28, 30, 34, 35, 36
Right superior temporal gyrus	56, −36, 14	.91	281	21, 22, 37, 42, 48
Smaller GMV and Decreased Activation In BPD				
Right inferior frontal gyrus, pars triangularis	50, 38 ,4	−.85	195	45, 46, 47, 48
Right inferior frontal gyrus, pars opercularis	50, 14, 26	−.82	333	4, 6, 43, 44, 48
Left postcentral gyrus	−44, −14, 52	−.80	297	3, 4, 6, 43, 48
Right parahippocampal gyrus	24, −4, 48	−.69	32	27, 37
Higher GMV and Enhanced Activation in BPD				
Right supplementary motor area	8, −18, 52	.84	139	4, 6
Cerebellum, vermic lobule IV/V	4, −54, −12	.71	195	18, 27, 30
Left precuneus	−4, −62, 36	.70	404	7, 23
Higher GMV and Decreased Activation in BPD				
Right middle frontal gyrus, dorsolateral	38, 18, 48	−.65	97	8, 9, 46

BA, Brodmann area; BPD, borderline personality disorder; GMV, gray matter volume; MNI, Montreal Neurological Institute.

regions might consequently underlie the emotional disturbances in BPD.

Regarding group differences in limbic regions, the left amygdala seems to be more strongly affected in BPD. Given the central role of the amygdala in the processing of salient and relevant information (60,61), hyperactivation of this region might reflect a greater salience of negative emotional stimuli for patients with BPD compared with HC. Additionally, our results suggest that psychotropic medication has a substantial impact on neural activations in a cluster comprising the left amygdala and hippocampus. Medication-free samples showed hyperresponsivity in response to negative stimuli compared with HC, whereas no such effect was found in BPD samples currently taking psychotropic medication. Thus, significant heterogeneity in the left amygdala findings can be partly explained by current medication status. The finding of normalized amygdala activity in medicated BPD patients might be associated with beneficial effects of medication on symptoms of emotional instability (25). This result also complements previous studies in major depression, which found depressive symptoms as well as hyperactivations of the amygdala to normalize with participants' intake of psychotropic medication (62,63). Still, this correlational finding must be confirmed by future studies, directly testing the effect of medication on limbic activity in BPD.

Apart from hyperactivity in the left amygdala to negative emotional stimuli, reduced brain activity was observed for the bilateral dlPFC in response to negative stimuli. Given the prominent role of the dlPFC in the cognitive control of emotions (64,65), these results are consistent with the conceptualization of BPD as an emotion regulation disorder. Specifically, we suggest that negative emotional stimuli impede dlPFC activation in BPD (i.e., lower activation in response to negative stimuli compared with neutral). This interpretation is reconcilable with the results of the comparison of within-group effects between patients with BPD and HC, which failed to observe group differences in dlPFC activation (Supplement 1). The independent group comparison of within-group effects was restricted to voxels showing significantly enhanced activation for negative compared with neutral conditions (i.e., negative > neutral). In contrast, the reported between-group interactions of emotion by group have no such restrictions and consequently include voxels with deactivations (i.e., neutral > negative) as well. Hence, our findings might provide a neural basis for impaired cognitive control when patients with BPD are confronted with negative emotional information (10,11).

Previous studies in health and psychopathology linked decreased functioning of the dlPFC to increased amygdala activity (66–68). Thus, dlPFC-amygdala abnormalities in BPD might be linked rather than independent from each other. Although these findings are suggestive of a functional relation, they still need to be complemented by functional connectivity studies to more strongly determine whether altered activity in the amygdala and dlPFC are indeed related (69–71). Interestingly, the dlPFC was recently shown to be subdivided into (at least) two main clusters: an anterior-ventral cluster and a posterior-dorsal cluster (72). Our findings mainly supported abnormalities in the posterior-dorsal parts in BPD, which was found to be involved in basic processes of cognitive control, such as the manipulation of sensory input and processing of contextual cues.

In addition to limbic hyperactivity in combination with attenuated activity of the dlPFC, relatively increased activations were also observed in the PCC. The PCC is implicated in processes of self-awareness and autobiographical memory (73). At first glance, functional hyperactivity of this brain region might thus be interpreted in terms of an increased self-relevance of negative stimuli. However, the PCC forms also an important node of the default mode network. Given that neither increased activation of the PCC during the processing of negative compared with neutral stimuli nor functional abnormalities between both groups were evident in the complementary analysis of within-group comparisons (Supplement 1), it is most likely that PCC abnormalities in BPD reflect an attenuated deactivation in response to the

baseline conditions. Recent findings support default-mode abnormalities in BPD with patients showing difficulties in switching between default-modes and task-related brain activations (74,75).

Structural Brain Abnormalities in BPD

The most prominent finding was reduced GMV of the right hippocampus in BPD. Although volume reductions were also present in the left hippocampus, this finding was less robust. As such, our findings partly replicate limbic abnormalities from previous meta-analyses (29,30). In contrast to previous work, only studies using automated segmentation procedures were included, which might limit statistical sensitivity in the detection of GM abnormalities (76). Volume reductions in the hippocampus have not only been found in BPD (29) but also in posttraumatic stress disorder (77), as well as in healthy adults with a history of childhood maltreatment (78), and would therefore be best interpreted as the result of traumatic stress. Interestingly, results also point to additional volume loss in a cluster comprising the hippocampus and amygdala as BPD patients increase in age. This finding was also observed in a region-of-interest based meta-analysis on structural brain abnormalities in BPD (79). The authors interpreted this finding as evidence of progressive hippocampal pathology, reflecting an interaction between early life stress and genetic vulnerability on the one hand and pathogenic effects of a heightened stress responses on the other (79).

Volume reductions were also detected in the subgenual ACC. This region is implicated in emotional processing, in contrast to more dorsal parts of the ACC, which are primarily associated with cognitive functions (80). Parallel to our functional imaging findings discussed above, one can additionally conclude that BPD patients exhibit abnormalities in the form of GMV reductions in key regions of emotion processing.

BPD patients showed relatively greater GMV than healthy control subjects in the right cerebellum, the supplementary motor area, the left posterior insula, and the right middle frontal gyrus (Brodmann area [BA] 9). Brodmann area 9 contributes to the dlPFC and was previously implicated in suppression of emotions and unwanted memories (74,75), unlike BA 46, which seems to reflect functional emotion regulation processes like reappraisal (76) and was found to be hypoactive in BPD. Considering that use-dependent brain plasticity might result in volume increases (78), GM abnormalities in BA 9 might be related to a greater use of emotion suppression in BPD (77).

Multimodally Affected Brain Regions

Functional brain abnormalities were found to overlap with structural brain abnormalities in BPD. Parts of the left amygdala and hippocampus were characterized by functional hyperactivity as well as smaller GMV. In contrast, both subregions of the dlPFC (BA 9, BA 46) showed higher GMV together with decreased activation.

A possible underlying factor for the relation between structural and functional abnormalities in limbic regions of BPD patients was investigated in a study of healthy adults (78). The authors demonstrated functional and structural alterations in healthy subjects with a history of childhood maltreatment, which are strikingly similar to the findings discussed above in BPD. First, a history of childhood maltreatment in healthy adults was related to higher amygdala reactivity during the processing of negative facial expressions. Second, dependent on the severity of aversive events in childhood, the authors found reduced GMV in the orbitofrontal cortex, hippocampus, and ACC (78). Since we found that GMV abnormalities in the amygdala are associated with functional hyperactivation, one could tentatively speculate that multiple stressful life events lead to structural changes by way of GMV loss, which necessitates hyperactivation of the amygdala.

Multimodal abnormalities were also identified in the vermis of the cerebellum, which is known to regulate individuals' autonomic responses and modulate limbic activations (81,82). Thus, cerebellar-limbic connections might be of further interest for the study of abnormal emotion processing in BPD.

Limitations and Outlook

Despite several strengths, there are some limitations that need to be considered. Our results indicate that abnormal functioning of dorsolateral prefrontal and limbic brain regions might underlie disturbed emotion processing in BPD. Although suggestive of a causal link, these findings need to be complemented by functional connectivity studies to more strongly determine whether altered activity in the amygdala and parts of the prefrontal cortex are functionally related (69–71). Second, the amygdala and hippocampus are two adjacent structures that are difficult to exactly demarcate with typical brain imaging field strengths (83). This might compromise the regional specificity of the abnormalities in the limbic system. Furthermore, most studies analyzed rather small data sets. Future studies with bigger sample sizes are needed to deflate between-study variance and provide increased statistical power (84). Findings of the multimodal analysis relied on independent data sets limiting potential inferences on how structural abnormalities contribute to functional abnormalities. Future research should aim to integrate these different approaches in the same sample of individuals (85,86). Combined with longitudinal studies, such approaches might help to disentangle etiologically related aspects of functional and structural changes in BPD.

Summary

In this meta-analysis, we report combined structural and functional neuroimaging findings in BPD. The results illustrate abnormalities in frontolimbic brain regions during emotion processing in BPD, which overlap with additional structural alterations. Current psychotropic medication was found to “normalize” limbic activity in BPD.

ACKNOWLEDGMENTS AND DISCLOSURES

No funding was provided for this project.

We deeply appreciate the help of all researchers who supported this project. In particular, we thank Sabine Herpertz, Anja Kraus, Annegret Krause-Utz, Gin Malhi, Michael Minzenberg, Kristin Prehn, Daniele Radaelli, Knut Schnell, and Moria Smoski for providing additional contrasts or statistical parametric maps from their studies. Their help allowed us to create an exhaustive, quantitative summary of emotion processing in borderline personality disorder.

In addition, we thank Catherine Hindi-Attar for valuable comments on a previous version of this manuscript.

The authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

From the Department of Clinical Psychology and Psychotherapy (LS), Freie Universität Berlin, Berlin; and Department of Psychosomatic Medicine and Psychotherapy (CS, IN), Central Institute of Mental Health Mannheim, Medical Faculty Mannheim/Heidelberg University, Mannheim, Germany.

Address correspondence to Lars Schulze, Ph.D., Freie Universität Berlin, Department of Clinical Psychology and Psychotherapy, Habelschwerdter Allee 45, Berlin 14195, Germany; E-mail: lars.schulze@fu-berlin.de.

Received Oct 15, 2014; revised Feb 27, 2015; accepted Mar 21, 2015.

Supplementary material cited in this article along with 3D neuroimaging content is available online at http://dx.doi.org/10.1016/j.biopsych.2015.03.027.

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