Archival Report

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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

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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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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.

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