Neural responses to emotional stimuli in comorbid borderline personality disorder and bipolar depression

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ABSTRACT

Borderline personality disorder (BPD) is a severe clinical condition characterised by different maladaptive traits such as impulsivity and affective lability. Mood and emotion dysregulation are core features of affective disorders. Indeed patients affected by mood disorder (MD) have a significantly higher prevalence of comorbid BPD, resulting in more unstable mood and poorer response to medication. Blood oxygen level-dependent functional magnetic resonance imaging has been used to investigate the neural correlates of emotional face processing. Images for each subject were entered into an analysis of variance (ANOVA) dividing participants into three groups (MD, MD+BPD, Controls). MD+BPD patients show lower activations in the dorsolateral prefrontal cortex and higher activations in the cingulate cortex and hippocampus. The present study identifies the neural basis of the interaction between BPD and MD. The lower rate of response to treatment in MD+BPD could be related to a more severe emotional dysregulation syndrome.

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compared with 45% of patients with MD alone (Kennedy et al., 2004; Newton-Howes et al., 2006). A common feature between mood disorders and personality disorders (cluster B) seems to be a dysfunctional level of emotion regulation. This theory is supported by different studies that underline cognitive distortion and emotional lability in both these conditions.

The neural bases of emotion have been the focus of considerable research. By administering blocks of stimuli with a positive or negative emotional tone, several research groups have defined regions of interest (ROIs) associated with the processing of affective stimuli and the cognitive generation of affect in depressed patients. The ROIs consistently activated include the cingulate cortex, prefrontal cortex, hippocampus and amygdala. Evidence suggests that fearful stimuli activate the amygdala, leading to activation of the cingulate cortex and dorsolateral prefrontal cortex. When information about a threatening stimulus reaches the amygdala, a series of neuroendocrine and behavioural responses occur, transmitting information to higher order cortical structures which, through a negative feedback loop, extinguish the emotional response (Brewin, 2001). A current model of emotion management proposes a circuit based on (1) controlling attention to, and (2) cognitively changing the meaning of, emotionally evocative stimuli. These two forms of emotion regulation depend upon interactions between the prefrontal and cingulate control systems and the cortical and subcortical emotion-generative systems (Ochsner and Gross, 2005).

Alterations in specific brain areas of this circuit could be worsened by a comorbid BPD; indeed epidemiological studies suggest that neural correlates of emotional instability in BPD and in mood disorder could partially overlap (Goldberg and Garo, 2009).

A study by Herpertz et al. compared amygdala activation during exposure to emotional stimuli in BPD patients and healthy subjects: while no activation of the amygdala was found in the control group, BPD patients showed high levels of activation, possibly in an attempt to mediate response to intense emotions (Herpertz et al., 2001).

The aim of the present study is to evaluate the neural basis of dysfunctional emotion regulation in a sample of bipolar depressed patients with and without a comorbid diagnosis of borderline personality disorder and age-matched controls.

2. Methods

2.1. Participants

Twenty-eight bipolar depressed patients (Type I) consecutively admitted into our inpatient unit, 14 with and 14 without a comorbid diagnosis of borderline personality disorder (DSM-IV criteria, SCID I and II interviews), and 17 age-matched controls were studied. Patients were receiving pharmacotherapy according to clinical need (Buspirone n = 3, venlafaxine n = 3; all patients were taking benzodiazepines). Exclusion criteria were mental retardation, substance abuse within the past 3 months, and history of major physical illness. Clinical and demographic characteristics are summarised in Table 1. Inclusion criteria were a baseline Hamilton Depression Rating scale (HDRS) score of 18 or higher. BPD diagnosis was made by trained psychiatrists using the SCID-II questionnaire.

All subjects underwent blood oxygen level-dependent functional magnetic resonance imaging (BOLD fMRI). After complete description of the study, written informed consent was obtained. The study protocol was approved by the local ethics committee.

2.2. Procedures

Neural correlates of implicit emotional processing of facial affect expressions were studied with a face-matching paradigm (Hairi et al., 2002) that delineated a network of brain structures including the amygdala and an extended regulatory network encompassing the cingulate, orbitofrontal, insular, and dorsolateral prefrontal cortices (Pezawas et al., 2005; Stein et al., 2007).

Four blocks of six pictures representing human faces with fearful or angry expressions interspersed with five blocks of geometric shapes were shown to the participants, who had to push a button on a response box to indicate which of the two images displayed in the lower side of the screen matched the one in the upper part. Gradient echo-planar images (fMRI) were acquired on a 3.0 T scanner (Gyrocscn Intera, Philips, The Netherlands) using a six-channel SENSE head coil. For each functional run, 124 T-weighted axial slices, parallel to the anterior commissure-posterior commissure (AC-PC) plane, were acquired using an EPI pulse sequence (TR (repetition time) = 3000 ms; TE (echo time) = 35 ms; flip angle = 90°; field of view = 230 mm; number of slices = 25; slice thickness = 5 mm; matrix size = 80 × 80 reconstructed up to 128 × 128 pixels). Two dummy scans before fMRI acquisition allowed us to obtain longitudinal magnetization equilibrium. Total time acquisition was 6 min and 11 s per trial. On the same occasion and using the same magnet 22 Turbo Spin Echo (TSE), 12 axial slices (TR = 1000 ms; TE = 85 ms; flip angle = 90°; field of view = 230 × 230 mm² field of view) were acquired parallel to the AC-PC plane to rule out brain lesions.

Images were computed, overlaid on anatomic images, and analysed using Statistical Parametric Mapping software (SPM2, Wellcome Department of Imaging Neuroscience, Institute of Neurology and the National Hospital for Neurology and Neurosurgery; London, England). We realigned the scans to correct for head movement. Images were then normalised to a standard EPI template volume based on the Montreal Neurological Institute (MNI) reference brain, and smoothed using a 10-mm full-width at half-maximum isotropic Gaussian kernel. The evolved hemodynamic responses were modelled as a delta function convolved with a hemodynamic response function and its temporal derivative within the context of the General Linear Model (GLM). At the individual level we first compared (t test, threshold p < 0.001) the face-matching condition with the shape-matching condition, thereby isolating regions that were engaged in the emotional processing of faces. Using the Wake Forest PickAtlas software (Wake Forest University, USA; www.fmri.wfu.edu), statistical maps were limited to prior regions of interest (ROIs) based on previous reports about the effective connectivity of brain structures activated by our task (Stein et al., 2007). The mask included the amygdala, hippocampus, anterior cingulate cortex [ACC; Brodmann’s area (BA) 24 and 32] and PFC (BA 9, 10, 11, 12 and 46). Contrasted images for each subject were then entered into second-level analysis of variance dividing participants into three groups: Controls, MD, MD+BPD. We also performed a correlation analysis of the HDRS with brain activation (Supplementary Material).

3. Results

Analysis of variance and post-hoc (Newman–Keuls test) analysis on behavioural data (reaction time, accuracy) failed to reveal any significant difference between groups (reaction time t = 10,000: MD + BPD = 4900,5.3 ± 6674.81, MD = 4915.67 ± 3069.53 and Controls = 4659.57 ± 2118.66, F = 1.319, p = 0.28; number of errors: MD + BPD = 0.21 ± 0.57, MD = 0.35 ± 0.18 and Controls = 0.11 ± 0.48, F = 0.39, p = 0.67).

In the whole sample the task significantly activated several brain regions pertaining to the a priori ROIs (Fig. 1). Maximal activations were detected in the cingulate cortex (BA 24, 31); other activations shared by all groups were detected in the dorsolateral prefrontal cortex (BA 9) and in the hippocampus. Including gender effect in the present analysis changed neither the activation nor the direction and effect size. Diagnosis markedly influenced the neural responses to the emotional task. The areas in the ROIs where the effect of diagnosis was significant are listed in Table 2 and plotted in Figs. 2–6; they include the cingulate cortex, DLPFC and hippocampus.

Mood disorder patients with BPD showed higher neural responses compared to controls in the cingulate cortex, while controls showed higher activations than patients in the DLPFC. Patients with mood disorder without a diagnosis of BPD showed an intermediate pattern of activation in both areas.

We also performed a post hoc analysis of the significant areas which confirmed brain activations, direction and effect size (data not shown).

Table 1: Clinical characteristics of the sample divided according to diagnosis.

<table>
<thead>
<tr>
<th>Age</th>
<th>Hamilton score</th>
<th>Age at onset</th>
<th>Duration of illness</th>
<th>No. depressive episodes</th>
<th>No. manic episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls: n = 17, M = 6.4</td>
<td>MD Patients: n = 14, M = 7.3</td>
<td>MD + BPD patients: n = 14, M = 4.5</td>
<td>p</td>
<td>Controls: n = 17, M = 6.4</td>
<td>MD Patients: n = 14, M = 7.3</td>
</tr>
<tr>
<td>45.41 ± 12.26</td>
<td>47.86 ± 8.19</td>
<td>43.27 ± 10.41</td>
<td>0.54</td>
<td>22.80 ± 4.18</td>
<td>23.71 ± 1.80</td>
</tr>
</tbody>
</table>

Data are mean ± standard deviations. MD = major depression; BPD = borderline personality disorder; M = male.
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