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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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1. Introduction

Borderline personality disorder (BPD) is a severe clinical condition characterised by different maladaptive traits such as impulsivity, aggressiveness, affective lability, self-injurious behaviours and identity problems.

BPD patients are unable to maintain stable relationships, and their volatility causes difficulties in social and occupational fields, with a 10% suicide prevalence, a rate 50 times higher than in the general population (Perry, 1993; Johnson et al., 2003; Black et al., 2004; Oldham, 2006).

In response to environmental events, BPD patients tend to react with extreme emotion. Indeed, the affective lability of BPD is characterised by marked sensitivity (low threshold) and strong reactions (high amplitude) to emotional stimuli that are abnormally slow in returning to baseline (long duration) (Gunderson and Zanarini, 1989; Linehan, 1993).

Emotions play an important role in coping strategies and in personality shaping. The BPD pattern of emotion regulation leads to an intense and fluctuating mood state that compromises directed behaviour and planning strategies.

Affective disorders, characterised by mood alteration and deficits in emotion regulation, present specific processing abnormalities resulting from dysfunctions in different brain areas (Davidson et al., 2002). Often patients affected by BPD suffer from a concomitant psychiatric syndrome. A recent study by Johnson, et al. (2003) has reported that 61% of BPD patients meet criteria for major depressive disorder, 35% for post-traumatic stress disorder, 29% for panic disorder and 13% for substance abuse disorder (Johnson et al., 2003). Similarly, as reported by Brieger et al., 38% of patients affected by bipolar disorders fulfill criteria for comorbid personality disorders among which the most frequent is BPD (Brieger et al., 2003). A recent review examining the research literature on this topic published between 1980 and 2006 found that bipolar patients have a significantly higher prevalence of axis II disorders with unstable mood; the authors concluded that bipolar patients with comorbid personality psychopathology have a poorer response to medication (Fan and Hassell, 2008). From a clinical point of view, it seems that one illness worsens the other; comorbidity with personality disorder seems to account for poor prognosis in major depression leading to chronic illness (Alnaes and Torgersen, 1997) and contributing to an increased lifetime suicide risk (Garno et al., 2005). A recent study by Ruggero et al. (2010) reported that fulfillment of diagnostic criteria for BPD frequently places patients at risk for being misdiagnosed with bipolar disorder (Ruggero et al., 2010).

Only a few studies have examined the influence of the BPD syndrome on major depression. Clinical experience suggests that people with dysfunctional personality traits tend to show a poorer response to antidepressant treatment (Sargant, 1966; Mulder et al., 2003; Mulder, 2004). About 55% of patients with concomitant BPD and major depression (MD) have an insufficient response to treatment

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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 concomitant BPD; indeed epidemiological studies suggest that neural correlates of emotional instability in BPD and in mood disorder could partially overlap (Goldberg and Garno, 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 (fluvoxamine $n=3$, 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.

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

	Controls ($n=17$, 6 M)	MD Patients ($n=14$, 7 M)	MD + BPD patients ($n=14$, 4 M)	p
Age	45.41 ± 12.26	47.86 ± 8.19	43.43 ± 10.41	0.54
Hamilton score	/	22.80 ± 4.18	23.71 ± 1.80	0.35
Age at onset	/	32.4 ± 8.07	28.00 ± 6.02	0.24
Duration of illness	/	11.7 ± 11.60	19.00 ± 7.46	0.16
No. depressive episodes	/	2.33 ± 1.32	5.14 ± 8.76	0.35
No. manic episodes	/	1.88 ± 1.69	5.00 ± 8.88	0.31

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

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 (Hariri et al., 2002) that previously 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 (EPI) were acquired on a 3.0 T scanner (Gyroscan Intera, Philips, The Netherlands) using a six-channel SENSE head coil. For each functional run, 124 T2*-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), T2 axial slices (TR = 3000 ms; TE = 85 ms; flip angle = 90°; turbo factor 15; 5-mm- thick, axial slices with a 512 × 512 matrix and a 230 × 230 mm^2 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 evoked 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.wfubmc.edu), statistical maps were limited to a priori 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 s × 10,000: MD + BPD = 49405.53 ± 6674.81, MD = 49154.67 ± 3069.53 and Controls = 46595.57 ± 2118.66, $F=1.319$, $p=0.28$; number of errors: MD + BPD = 0.21 ± 0.57, MD = 0.35 ± 1.08 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, BA 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).

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