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Mirror neuron activations in encoding of psychic pain in borderline personality disorder

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ABSTRACT

Borderline personality disorder (BPD) is characterized by pronounced emotional instability in interpersonal relations. Previous studies have shown increased activity in the amygdala, an imaging phenotype of negative affect. However, clinical accounts of BPD have drawn attention to deficits in social cognition and their likely role in engendering emotional instability. BPD patients show enhanced sensitivity to other people's emotions, while being less proficient in reading motives and reasons. In the present functional imaging study, we exposed BPD participants to stylized scenes of individuals affected by loss or separation, an issue to which these patients are particularly sensitive. Previously shown to activate the mirror neuron system, these mourning scenes were here also used to assess differential amygdala activity in stimuli of negative valence, but low arousal. Relative to controls, BPD patients were found to activate sensorimotor areas, a part of the mirror neuron system thought to encode basic aspects of the perception of motoric activity and pain. This contrasted with the activity of areas related to more complex aspects of social cognition, such as the inferior frontal gyrus. The amygdala was more active in patients when viewing these scenes, but this effect also showed a strong association with levels of depressiveness and neuroticism. After adjusting for these covariates, differences in amygdala activation were no longer significant. These findings are consistent with models of social cognition in BPD that attribute emotional sensitivity to emotional contagion through the mirror neuron system, in contrast to areas associated with more sophisticated forms of social cognition. These effects were accompanied by increased amygdala reactivity, consistently with the common occurrence of affective symptoms in these patients.

1. Introduction

Borderline personality disorder (BPD) is characterized by emotional and behavioural instability (Gunderson and Singer, 1975; Skodol et al., 2002), high levels of negative affect and depressive symptoms (Perry, 1985; Comptois et al., 1999; Levy et al., 2007) and negative representations of self and others (Bender and Skodol, 2007). Current neurobiological models of BPD (Linehan, 1993; Herpertz et al., 2001; Skodol et al., 2002) suggest that emotional instability might be responsible for key symptoms of instability in mood, self-image, and behavior, such as impulsivity, self-harm, and unstable relationships.

Two possible (but not necessarily incompatible) accounts have been proposed in the clinical neurosciences to account for the symptoms of BPD. The first account views emotional dysregulation as its key component, in common with other disorders of affect. In support of this account, functional neuroimaging studies have identified a possible phenotype of emotional instability in the hyper-reactivity of the amygdala to highly arousing and negative emotional stimuli (Herpertz et al., 2001; Donegan et al., 2003; Minzenberg et al., 2007; Koenigsberg et al., 2009a; Swartz et al., 2015; for reviews and meta-analyses, see Schulze et al., 2015). This neuroimaging phenotype is shared with other disorders of affect, including depression (Whalen et al., 2002; Hariri and Whalen, 2011; Stuhrmann et al., 2011).

A second account draws attention to deficits in social cognition in BPD (Kernberg, 1967; Gunderson, 2007; Hill et al., 2008; Fonagy et al., 2017). Social cognition is a necessary requirement for successful interpersonal functioning. It refers to the ability to adequately recognize social signals, the context they are placed in, and relevant affective responses (Frith and Frith, 2003), with possible consequences on one's capacity to regulate emotion (Messina et al., 2016). In this second account, deficits in social cognition and the resulting difficulties in the interpretation of social cues lie beneath interpersonal and emotional

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dysfunction (for reviews of evidence on these deficits, see Dinsdale and Crespi, 2013; Roepke et al., 2013). Patients suffering from BPD often misinterpret communication of others, for example by attributing to them negative intentions. Social dysfunction in BPD is thought to emerge in a developmental context (Gunderson and Lyons-Ruth, 2008; Hill et al., 2008), where dispositional factors interact with negative experiences of abuse and adverse parenting styles (Zanarini et al., 2002; Belsky et al., 2012). In this account of BPD, these early experiences durably affect adult emotional functioning in the form of disorganized interpersonal relationships (Steele and Siever, 2010; Fonagy and Luyten, 2009).

In the neurobiological study of social cognition, a distinction may be made between cortical areas involved in a relatively automatic encoding system on the one hand, and those associated with sophisticated inferences on the reasons for the actions of others on the other. Areas involved in the former and more basic type of social cognition include the mirror neuron system (Rizzolatti and Fogassi, 2014; Keysers et al., 2010). In neuroimaging studies, these areas are active both when experiencing or performing an action and when observing it. This mechanism ('shared representations') also operates in the somatosensory and insular cortices, which are active when observing others being touched and when being touched oneself (Keysers et al., 2010; Bufalari and Ionta, 2013), and in studies of empathy for pain (Lamm et al., 2011; Lamm and Majdandzic, 2015). These findings motivate the use of passive exposure paradigms in functional neuroimaging to investigate the neural substrates encoding aspects of the emotional experience of others in psychopathological conditions (Dapretto et al., 2006; Meffert et al., 2013). Somatosensory and posterior insular regions are also involved in emotion recognition grounded in physical features, such as the identification of facial expressions (Adolphs et al., 2000; Operskalski et al., 2015; Viviani et al., 2018). Taken together, these observations suggest the importance of the mirror system in encoding emotion from cues that are directly observable (Cross et al., 2016) and in less reflective forms of empathy, such as emotional contagion (Frith, 2007). In contrast, the type of social cognition often referred to as mentalization or theory-of-mind (Saxe and Kanwisher, 2003; Frith and Frith, 2003; Fonagy and Luyten, 2009) refers to the ability to read the reasons for the behavior of others and take them into account in one's own responses to manage interpersonal relations. Neuroimaging studies suggest the involvement of the temporo-parietal junction and the ventromedial prefrontal cortex in theory of mind (Saxe and Kanwisher, 2003; Frith and Frith, 2003). Another cortical area identified in the literature is the right inferior frontal gyrus, which is associated with encoding the meaning of an observed action through the context in which it takes place (Carr et al., 2003; Iacoboni et al., 2005; Kaplan and Iacoboni, 2006).

Revisiting the issue of emotional instability in interpersonal interactions in view of these insights, Ripoll et al. (2013) have suggested that, since the deficits in BPD affect theory of mind specifically, corresponding changes in activation of neural substrates should be observable at this more sophisticated level, which they referred to as 'mental state attribution'. In contrast, they suggested that the high emotional reactivity of BPD is compatible with enhanced activation of relatively automatic social cognition components such as the premotor and somatosensory cortices (Keysers et al., 2010). This model is consistent with the evidence that BPD individuals are more sensitive to emotional information (Krause-Utz et al., 2012; Winter, 2016; Harari et al., 2010; Meehan et al., 2017), showing enhanced emotional contagion (Niedtfeld, 2017), but may be less proficient than healthy controls in labeling their own emotions (New et al., 2012) or assess reasons for behavior of others in the context of social interactions (Minzenberg et al., 2006; Preißler et al., 2010).

Using functional imaging, Dziobek et al. (2011) have provided evidence consistent with this dissociation. In a task in which participants were instructed to attend to the social-cognitive aspects of emotional pictures, they reported stronger activations in the somatosensory cortex in BPD patients, while activations in the inferior frontal gyrus were present in healthy controls. Likewise, in a task that included emotion recognition and affective theory of mind, Mier et al. (2013) detected higher sensorimotor cortical activation in BPD, while healthy controls preferentially activated the inferior frontal gyrus (BA44; for a review, see Mitchell et al., 2014). Using a formalized social exchange game, King-Casas et al. (2008) showed that BPD individuals were impaired in maintaining or repairing cooperation with a partner. BPD individuals followed a simple tit-for-tat retaliation strategy when cooperation was threatened, while healthy individuals attempted repair by renewing efforts at cooperation. Behavior in the healthy group was associated with activity in the anterior insula, extending into the inferior frontal gyrus, that encoded social norm violations in the partner in the context of uncertainty in social interactions. Within an interpretive framework centred on mentalization, this finding is consistent with healthy individuals forming models of their counterparts in the game open to different potential outcomes and influences, while little or no modeling is required by the simple reciprocation strategy of BPD. These findings and the notion of context invoked to explain inferior frontal gyrus involvement in studies of encoding of actions (Iacoboni et al., 2005) suggest the importance of this region in the encoding of the stimuli within abstract models of motives or of social interactions that are themselves not directly perceivable. This interpretation complements the insight of classic neuroimaging studies showing activation in the inferior frontal gyrus being associated with semantic complexity (Demb et al., 1995; Thompson-Schill et al., 1997).

In the present functional neuroimaging study we assessed the differential activation of neural substrates of social cognition in BPD using a passive exposure paradigm in which participants viewed stylized drawings of scenes of mourning individuals compared to neutral pictures (Labek et al., 2017, Fig. 1). The passive view setting is the same used by most previous studies of borderline pathology or other affective disorders, but the nature of the images to which participants are exposed introduces significant differences. First, although the content is of marked negative valence (mourning), the arousal value of these images, in which facial features are absent, was rated from average to low in healthy subjects (Labek et al., 2017). This is in contrast to emotional images typically used in neuroimaging studies of amygdala reactivity, which depict faces with emotional expressions or aversive scenes. While these studies rely on high emotional salience to evoke a response in the amygdala, the rationale for the use here of the mourning scenes is the thematic importance of issues of loss and abandonment in BPD (Steele and Siever, 2010).

Second, as shown in a previous study, these images elicit the activation of several neural substrates of social cognition (including the somatosensory cortex, Labek et al., 2017). This study also showed that exposure to the mourning images resulted in progressive recruitment of the inferior frontal gyrus (BA44/45), detectable in the time trend during the experiment. A possible interpretation of this finding is that participants were progressively composing a representation of the context of emotional experience that these scenes depict. This may be due to the fact that contextual cues were important to correctly interpret the scenes. These previous findings suggest that it may be possible to simultaneously assess the activation of the mirror neuron system and the differential recruitment of contextual or schematic information that would refer to latent properties of the scenes and may not be inferred primarily from sensory features alone. Hence, an issue we wished to address here is evidence for a mechanism for the simultaneous increase in emotional sensitivity/contagion and decrease in mentalizing/mental attribution in BPD. If the mechanism of emotional sensitivity/contagion observed in BPD is mediated by the mirror neuron system as hypothesized by Ripoll et al. (2013), we should expect higher activity in cortical areas that are part of this system in BPD patients. In contrast, deficits in mentalization/mental state attribution should be visible in reduced recruitment of areas associated with context representation, such as the inferior frontal gyrus in our paradigm.

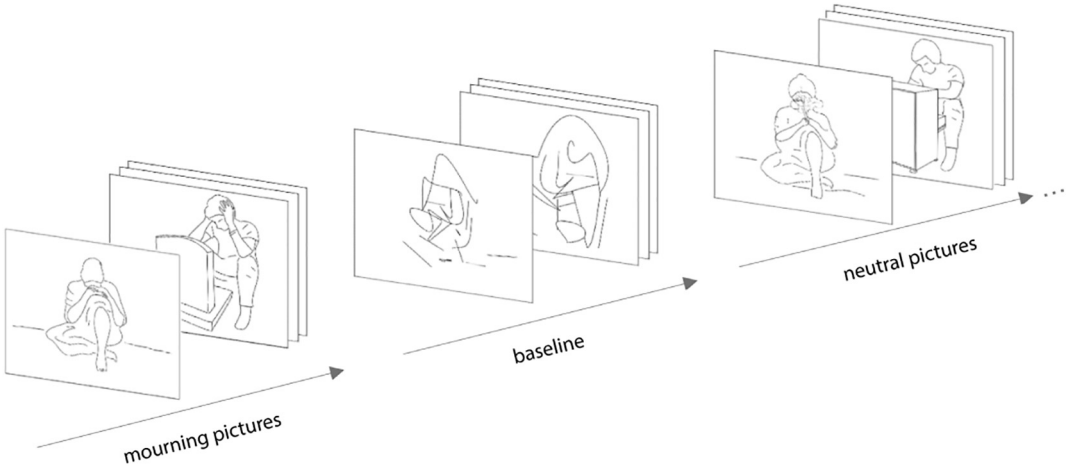

Fig. 1. Schematic representation of the passive exposure task.

Table 1
Demographics and clinical characteristics of study sample.

	BPD patients (n = 20)		HC (n = 20)		p
	Mean	SD	Mean	SD	
Age (years)	24.9	5.26	26.05	5.96	n.s.
CES-D	34.05	2.80	8.70	1.28	< 0.001
NEO-FFI Neuroticism	39.5	3.20	16.0	2.01	< 0.001
CTQ total	66.85	2.95	34.55	1.68	< 0.001

Note. BPD: Borderline personality disorder; HC: healthy controls; n: number of subjects; SD: standard deviation; CES-D: depressiveness; NEO-FFI Neuroticsm: NEO-Five-Factor-Inventory, subscale Neuroticism; CTQ: Childhood Trauma Questionnaire.

Our study also offers the opportunity to investigate the signal in the amygdala in negatively valenced but not overly arousing stimuli in BPD, an issue relevant for the account based on amygdala reactivity. The effect of negative valence alone has not been investigated in previous functional imaging studies of BPD. In this respect, a second issue we wished to address is the relative contribution in BPD of depressiveness or the generic propensity to appraise events in the environment negatively in amygdala activation. This may be of interest since, given its shared occurrence in both BPD and depression, the increased amygdala reactivity phenotype may refer to a transdiagnostic symptom domain of negative affect (Sanislow et al., 2010) reflecting long-term motivational consequences of early exposure to adversity (Dannlowski et al., 2012, 2013; van Harmelen et al., 2013). Hence, we included ratings of depressive mood and neuroticism in our models to assess state and trait individual differences in this domain.

Exposure to these images may therefore allow us to assess recruitment of neural substrates associated with two distinct symptom domains of BPD, affective/emotional dysregulation and deficits in social cognition. The rationale for looking at these two intermediate phenotypes simultaneously is to allow for a dimensional conceptualization of this personality disorder.

2. Material and methods

2.1. Participants

The study sample consisted out of 20 female patients with BPD and 20 healthy female controls between 18 and 40 years (mean age 25.48, std. dev. 5.62). All participants were right-handed. BPD patients were in- and out-patients from the Department of Psychiatry and Psychotherapy III, Ulm University, Germany. Healthy controls were recruited from the community. The psychiatric status was conducted by trained clinical psychologists according to DSM-IV criteria using the German version of the Structured Clinical Interview for DSM-IV axis-II disorders (SCID-II, Fydrich et al., 1997) and the German version of the Mini International Neuropsychiatric Interview (M.I.N·I, Sheehan et al., 1998) for axis-I diagnoses. Furthermore, all participants completed the German version of the Center for Epidemiological Studies Depression Scale (CES-D; German version: Allgemeine Depressionsskala, ADS, Hautzinger and Bailer, 1993), the subscale Neuroticism of the German version of the NEO-Five-Factor Inventory (NEO-FFI, Borkenau and Osterndorf, 1993), and the German version of the Childhood Trauma Questionnaire (CTQ, Bernstein and Fink, 1998). These scales assessed negative mood state, a trait representing the tendency to react to potentially negative cues, and the occurrence of negative events in childhood.

Detailed demographic, diagnostic and psychometric data are shown in Table 1. Almost all patients (18 out of 20) were on a stable antidepressant drug regime (monotherapy or combination of medication) for at least two weeks prior to scanning, which included escitalopram (n = 1), citalopram (n = 2), fluoxetine (n = 5), sertraline (n = 6), venlaflaxine (n = 3), mirtazapine (n = 1), opipramol (n = 1), and trimipramine (n = 1). Antipsychotic medication on demand was allowed and present in 10 out of the 20 patients, but was required to pause for at least two half-lives prior to the fMRI scan. Exclusion criteria for the BPD patients were life-time bipolar-affective disorder, life-time schizophrenia, current substance abuse disorder, and antipsychotic long-term medication. Exclusion criteria within the healthy control group were any substantial manifestation of BPD and any lifetime or presence of Axis I and Axis II disorders according to DSM-IV-TR criteria. Formally, participants in the control group were required not to satisfy the SCID-II criteria for BPD, which require 5 or more criteria in this diagnostic category. The sample of participants who volunteered of the study contained no individual that satisfied any criterion fully; two participants fulfilled one criterion partially (score 2 in the evaluation form), and one participant fulfilled two criteria partially. Exclusions criteria for both groups were major somatic or neurological disorders and general contradictions to MRI scanning. BPD symptom severity in the patients group, as assessed with the SCID-II, averaged at 6.85 (s.d. 1), and ranged from 5 to 9 (which is the maximal score in this nosologic category). Notwithstanding the occurrence of individuals with mild or severe pathology, the sample was relatively homogeneous, with 50% of patients scoring at average severity, and only two 2 individuals attaining the maximum score, reflecting recruitment criteria that led to the exclusion of severe cases. Axis I co-morbidity in the BPD group, as assessed with the SCID-II, included 11 patients with current symptoms of major depression, two with lifetime major depression, five with dysthymia, nine with anxiety disorder (panic disorder: n = 1,

agoraphobia: n = 4, social phobia: n = 3, general anxiety disorder: n = 1), ten with posttraumatic stress disorder, one with an eating disorder (bulimia nervosa), and three with past drug and alcohol abuse. There was no significant association between intensity of BPD symptoms (as assessed with the SCID-II) and intensity of depressiveness (CES-D scores, $r = 0.04$, $t = 0.16$, n.s.) or neuroticism (NEO-FFI, $r = 0.28$, $t = 1.25$, p = .11). This null finding might be due to the low variability of the SCID-II scores in this sample. The study was approved by the local ethics committee (Ulm University, Germany) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

2.2. Neuroimaging task

Participants were exposed to alternating blocks of scenes depicting individuals reacting to loss and scenes with neutral content, as described previously (Labek et al., 2017). Facial expressions were absent in the mourning scenes, and body posture was approximately replicated in the neutral control scenes. Salience and valence ratings of these pictures in the healthy were reported in the original publication. The blocks were separated by intertrial intervals in which scrambled drawings were shown. These scrambled drawings replaced the traditional display of a fixation cross to prevent participants from reminiscing about the content of the scenes previously seen. Each block or intertrial interval was composed of a set of 4 pictures with content reflecting the block type, each shown for 3 s., resulting in blocks and intertrial intervals of 12 s. each. There were 4 blocks with mourning scenes and 4 blocks of control scenes. Participants were instructed to observe the scenes presented during the task.

2.3. MRI data acquisition

Data were collected on the premises of the Department of Psychiatry and Psychotherapy III, Ulm, using a Prisma 3 T scanner (Siemens, Erlangen, Germany) equipped with a standard 64-channels coil. Participants were placed in supine position with their head padded to minimize movement artifacts during data acquisition. Participants were permanently in contact with the experimenter during the acquisition and could interrupt it at any time. Pictures were projected onto a screen located behind the scanner, which participants could view through a mirror mounted on the head coil. The presentation of trials was programmed in standard software (Presentation 14, Neurobehavioral Systems Inc., Albany, CA). A T2*-sensitive echo-planar imaging sequence was used (TR/TE: 2460/30 ms, flip angle 90°, 64 × 64 pixels, FOV 24 cm, 39 2 .5mm slices with a gap of 0 .5mm, giving an isotropic pixel size of 3 mm).

2.4. MRI data analyses

Statistical modeling and analysis was conducted with the freely available software SPM12 (Functional imaging laboratory, University College London, www.fil.ion.ucl.ac.us/spm) running on MATLAB (version 12, The MathWorks, Natick, MA). The first 6 images were discarded to allow for equilibration effects. After realignment and normalization to a standard MNI template, data were resampled at the isotropic voxel size 2 mm and smoothed with a Gaussian kernel (FWHM 8 mm). At the first level, blocks showing mourning and control scenes were separately modeled with box-car functions convolved with a standard BOLD response curve. Realignment parameters were included as nuisance covariates. The first-level model included an autoregressive term (AR(1)) to account for the autocorrelation of the residuals. In a second model, these regressors were complemented by parametric modulations of the time trend, as in Labek et al. (2017). These regressor sets were used to estimate three contrasts: of the scenes versus the implicit baseline of the scrambled images (task), of mourning versus control scenes (effect of mourning), and of the time trend in the mourning blocks. The appropriate contrast images were brought to the second level to account for subjects as a random factor. At the second level, patient group provided the main regressor of interest. Age, depressiveness levels (CES-D) and neuroticism (NEO-FFI) were standardized and used as confounding covariates. Region of interest (ROI) analyses in the amygdala were conducted using data reported in Amunts et al. (2005), while the 'aal' atlas (Tzourio-Mazoyer et al., 2002) was used to form a mask for right BA44/45 and for designations of cortical areas. Significance levels obtained with a ROI correction are identified explicitly as such in the Results section; all other significance levels are corrected for the whole volume. All coordinates reported in the study are Montreal Neurological Institute (MNI) coordinates.

For inference, we report significance levels corrected at the peak and cluster level. For peak-level correction, significance levels based on random field theory are reported, as provided by the SPM12 software. Cluster-level corrections were computed by permutation (Holmes et al., 1996) using a cluster-defining threshold of $p < .001$, uncorrected, for the whole volume, and $p < .01$, uncorrected, for ROI analyses. Threshold-free cluster enhancement (TFCE) corrections of Table 1, introduced by Smith and Nichols (2009), were computed by permutation using the recommended settings (H = 2.0, E = 0.5, volume approximation through intervals of 0.1). Overlays were produced with the freely available software MRIcron (http://people.cas.sc.edu/rorden/mricron/index.html).

3. Results

Differences between BPD individuals and controls were assessed in three contrasts of interest: pictures (mourning or neutral) vs. baseline, mourning pictures vs. neutral control pictures, and the time trend in the exposure to the pictures.

3.1. Mourning and neutral pictures vs. scrambled pictures

The contrast of both picture types (mourning and control) vs. scrambled pictures (viewing task vs. implicit baseline) revealed no significant activation differences between the BPD group and healthy controls when corrected for the whole brain.

Previous neuroimaging studies of BPD using a passive exposure to emotional images reported increased activation of the amygdala in the task vs. baseline contrast (Donegan et al., 2003; Koenigsberg et al., 2009b). We therefore assessed differential activation of the amygdala through a predefined anatomical region of interest (ROI) analysis. Compared to healthy controls, BPD individuals showed a weak activation of the amygdala that failed to reach significance after correction for the ROI (x, y, z: 26, 2, −18, $t = 3.21$, p = .122, peak-level corrected; p = .31, cluster-level corrected). We noted, however, that in this model (i.e., while including the regressor for BPD diagnosis) the amygdala was significantly active as an effect of depressiveness and neuroticism (x, y, z: 24, −12, −14, partial correlation $r = 0.60$, $t = 3.95$, p = .024, peak-level, and p = .10, cluster-level ROI corrected). This activation extended posteriorly into the anterior hippocampus (x, y, z: 24, −16, −16, $r = 0.68$, $t = 4.87$; −20, −20, −16: $r = 0.54$, $t = 3.38$, $p < .001$, uncorrected). Since BPD individuals scored higher in depressiveness and neuroticism than healthy controls, they may have displayed amygdala hyperactivity when tested without adjustment for these rating scales. This was indeed the case (x, y, z: 24, −10, −12, $t = 4.43$, p = .007, peak-level ROI corrected; p = .012, cluster-level corrected, Fig. 2). As illustrated in this figure, relative to the scrambled pictures, the amygdala was more active in BPD not only in the mourning condition (22, −8, −12, $t = 3.39$, p = .001, uncorrected) but also in the control condition (26, −10, −12, $t = 3.21$, p = .001, uncorrected). Within the BPD group, there was no significant effect of CTQ scores on the activity of the amygdala (x, y, z: −24, −8, −22, $r = 0.38$, $t = 1.74$, n. s.) or in the full brain. This was also the case for all contrasts examined below.

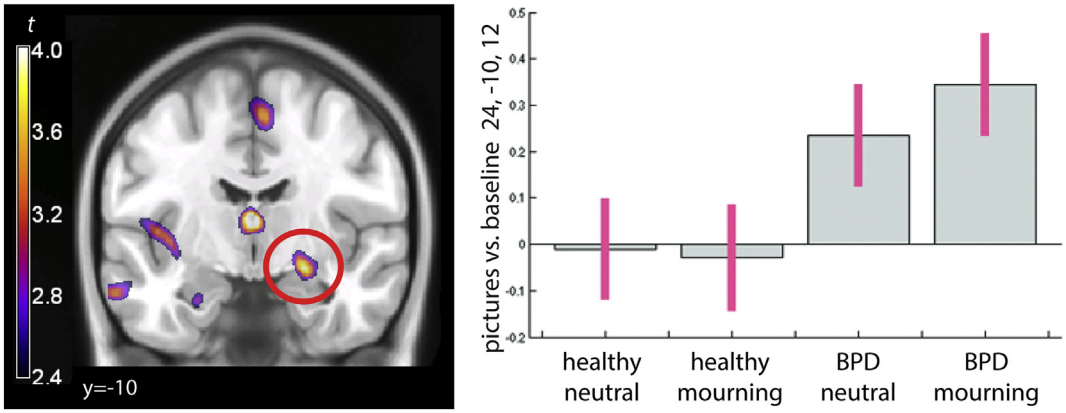

Fig. 2. Left: effect of pictures vs. baseline in the right amygdala, overlaid on a template brain. For display purposes, *t* maps were thresholded at p < .01, uncorrected. Slice location shown in MNI coordinates. Right: effect size shown separately in healthy controls and BPD individuals in neutral and mourning pictures.

3.2. Mourning pictures vs. neutral pictures

When testing for the effect of mourning pictures (irrespective of group), we replicated the bilateral activation of the middle and superior temporal gyrus (x, y, z: −54, −20, 2, $t = 6.52$, p = .005, peak-level, and p < .001, cluster-level corrected for the whole brain) as well as of the posterior cingulus-precuneus (x, y, z: 6, −46, 22, $t = 8.50$, p < .001, and − 4, −28. 32, $t = 6.91$, p = .002 and p < .001, same corrections) reported in the previous study (Labek et al., 2017). These areas were not modulated by the interaction of this contrast with the BPD group.

However, in the same interaction, BPD individuals compared to healthy controls exhibited increased activation in a cluster comprising the left sensorimotor cortex and the left dorsal posterior insula (Fig. 3 and Table 2, cluster 1). BPD individuals were also more active in several smaller clusters in the somatosensory cortex and in the middle cingular cortex (cluster 7), without however reaching significance (Table 2). This finding, obtained while adjusting for depressiveness and neuroticism, was confirmed in a model without these confounding covariates (not shown for brevity).

In the amygdala ROI analysis, there was no significant activation of BPD individuals compared to healthy controls (x, y, z: 22, −6, −12, $t = 2.03$, p = .025, uncorrected). In the same model, the effect of depressiveness and neuroticism in the amygdala was stronger (x, y, z: 24, −2, −26, $r = 0.49$, $t = 3.32$, p = .096, peak-level, and p = .046, cluster-level ROI corrected). However, as in the previous analysis, when we tested the interaction with BPD group without adjusting for depressiveness and neuroticism, a significant effect was detected (x, y, z: −18, 2, −26, $t = 3.65$, p = .044, peak-level, and p = .134, cluster-level ROI corrected).

3.3. Time trend over blocks

This contrast was estimated to test the hypothesis, based on the results of the previous study with this paradigm (Labek et al., 2017), of a modulation of the inferior frontal gyrus (BA44/45) with less pronounced effects in BPD individuals.

Prior to testing this hypothesis, we verified that we could replicate the findings of the previous study irrespective of group. We detected an effect of a positive trend in the right inferior frontal gyrus in BA44/45 (x, y, z: 60, 18, 26, $t = 4.02$, p = .056, peak-level, and p = .015, cluster-level ROI corrected). In this same ROI, there was limited evidence for a reduction of this effect in BPD individuals (x, y, z: 50, 30, 8, $t = -3.35$, p = .23, and p = .057, cluster-level ROI corrected). The effect for reduced activation in BPD was stronger on the left side (x, y, z: −44, 20, 16, $t = -4.69$, p ≤ .001, uncorrected). However, in the

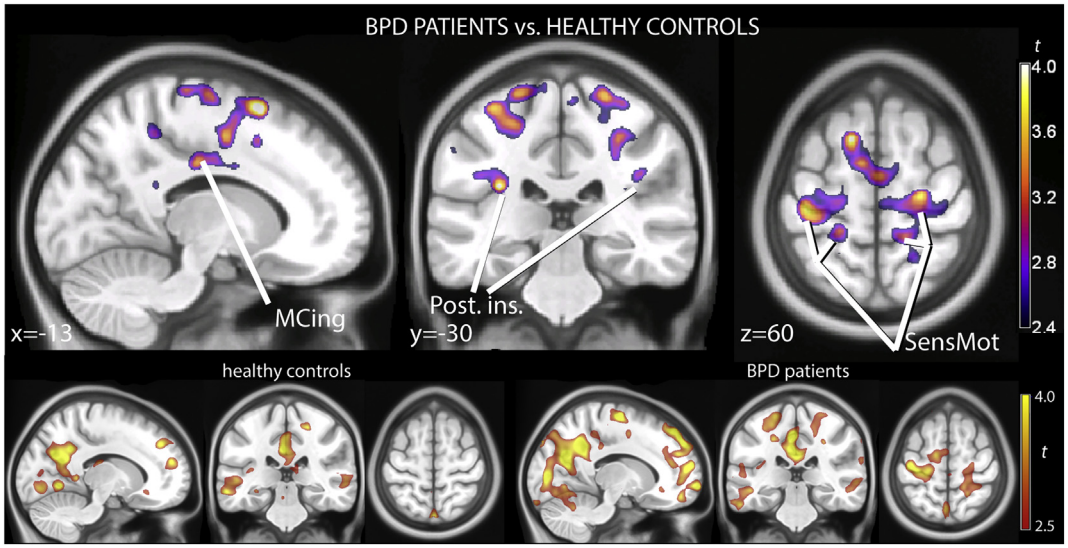

Fig. 3. Contrast BPD individuals vs. healthy controls for the mourning vs. neutral pictures comparison (top row), overlaid on a template brain. Bottom row: separate comparisons for the healthy and BPD groups. For display purposes, *t* maps were thresholded at p < .01, uncorrected. Slice locations shown in MNI coordinates. MCing; middle cingular cortex; Post. ins.: posterior insula; SensMot: sensorimotor cortex.

Table 2
Mourning vs. control in BPD compared to healthy controls.

Cluster #	Location	MNI coord.			*k*	p clust.	*t*	p peak.	p (TFCE)
1	Postcentral/precentral Gyrus (BA 4/6)	−36	−22	54	255	0.045	4.30	0.736	0.046
	Posterior Insula	−32	−30	22			4.19	0.816	0.050
2	Precentral Gyrus (BA 6)	22	−24	70	126	0.127	4.49	0.572	0.055
		24	−18	58			3.88	0.964	0.064
3	Supp. Motor Area (BA 6)	−6	8	66	114	0.144	4.42	0.635	0.049
		−14	12	62			4.39	0.658	0.049
4	Precentral Gyrus (BA 6)	−20	−12	66	82	0.198	3.92	0.953	0.052
		−22	−22	68			3.57	0.998	0.055
	Postcentral Gyrus (BA 3/4)	−22	−34	68			3.58	0.998	0.055
5	Putamen	26	0	18	66	0.250	5.41	0.088	0.064
6	Postcentral/Supramarg. Gyrus (BA 3)	58	−20	38	32	0.426	3.96	0.941	0.099
	Supramarg. Gyrus (BA 2/40)	66	−20	40			3.95	0.944	0.099
7	Mid. Cingulus (BA 23/24)	−10	−4	46	39	0.374	3.67	0.994	0.063
	Supp. Motor Gyrus (BA 6)	−8	0	56			3.59	0.998	0.064
8	Mid. Frontal Gyrus (BA 9)	−22	46	32	35	0.403	4.09	0.881	0.303
9	Precentral Gyrus/Paracentral lobule (BA 4/6)	−8	−24	72	34	0.405	4.00	0.926	0.057
		−8	−14	70			3.50	0.999	0.060
10	Supp. Motor Area (BA 6)	2	−8	62	29	0.453	3.78	0.984	0.060

Note. Reported peaks are at least 4 mm apart. Peaks located in the same brain area within the same cluster are indicated by blanks in the Locations column. BA: Brodmann Area; MNI coord.: Montreal Neurological Institute coordinates (in mm); *k*: cluster extent (in voxels of isotropic size 2 mm); p clust.: significance level, family-wise-error cluster-level correction (permutation test); *t*: Student's t; p peak.: significance level, family-wise-error peak-level correction (random field theory correction); p (TFCE) significance level, threshold-free cluster enhancement correction (permutation test); Prim., Supp., Supramarg., Mid.: primary, supplementary, supramarginal, middle.

model without the confounding covariates of depressiveness and neuroticism, this effect was less pronounced (−44, 18, 18, $t = -2.15$, $p = .019$, uncorrected).

4. Discussion

In the analysis of the imaging data, the BPD group differed from the control group in several respects. First, the amygdala was more active in BPD individuals while passively viewing the scenes in comparison with the condition of scrambled images. This result is consistent with the findings of the functional imaging literature that used highly arousing emotional scenes to assess amygdala reactivity in borderline pathology. Several studies have detected a difference in the patients group in the comparison with the baseline (Donegan et al., 2003; Koenigsberg et al., 2009a). As in previous studies (and consistently with the descriptive psychopathology of BPD), our patients had high levels of depressive symptoms and neuroticism levels. When adjusted for these symptoms, the higher activation of the amygdala was no longer detected, suggesting a role of affective symptoms, consistently with the literature on amygdala activity in affective disorders more generally. This finding, however, should be interpreted with caution, given the differences in depressiveness between BPD individuals and controls, reflecting the frequent co-morbidity of BPD with depression, which make the regressors collinear. It has been argued that high levels of depressive symptoms are constitutive of this personality disorder irrespective of the presence of a clinical depressive episode (Levy et al., 2007) due to the propensity of BPD individuals to activate traces of past negative interpersonal experiences. Likewise, the tendency to interpret ordinary events as threatening that characterizes neuroticism is common among BPD individuals (Clarkin et al., 1993), and is the personality trait that best discriminates between them and controls (Morey and Zanarini, 2000). Our findings suggest that amygdala reactivity might be a phenotype of negative affect that may be part of but not necessarily specific to BPD. This conclusion is consistent with a transdiagnostic symptom domain perspective (Sanislow et al., 2010).

Second, BPD individuals activated somatosensory and premotor cortices more than controls when viewing images of mourning scenes in comparison with the control scenes. This activation extended medially to the middle cingular cortex, an area detected in neuroimaging studies of grief (Gündel et al., 2003; Kersting et al., 2009). In contrast to the effect in the amygdala, this activation was not associated with levels of depressiveness and neuroticism. Consistently with the distinction between the symptom domains of emotion dysregulation and social cognition, the amygdala and the secondary somatosensory cortex appear to play distinct but complementary roles in emotion recognition (Adolphs, 2002). Together with the dorsal posterior insula, which was also relatively more active in this contrast and is structurally and functionally related (Kurth et al., 2010), these somatosensory regions have been shown to encode basic levels of pain representations (Lamm et al., 2011). In studies of the mirror system activated by observing human action, activity in this area is thought to occur relatively automatically and to reflect the basic perception of action schemas (Iacoboni et al., 2005) and emotional contagion (Frith, 2007). Furthermore, this finding replicates a previous observation by Mier et al. (2013). Using a task of social cognition, they reported increased recruitment of sensorimotor regions in BPD. This increased activity is consistent with the hypothesis that cortical areas concerned with the relatively automatic encoding of sensory and emotional aspects of experience may be more active in BPD than in controls reflecting the high level of emotion expressed by these individuals in social interactions.

Finally, although the data were consistent with increased recruitment of the inferior frontal gyrus in control subjects, the evidence in this respect was too weak to draw definitive conclusions. This limited evidence, however, is consistent with the findings of Mier et al. (2013), who were able to demonstrate increased recruitment of this region in healthy controls, similar to Dziobek et al. (2011). A similar finding was reported by Schulze et al. (2011) in the context of a reappraisal task. There are several candidate explanations of the weakness of our finding in the right inferior frontal gyrus. One is that, in contrast to Mier et al. (2013), we relied on passive exposure to our stimuli instead of providing explicit instructions directing individuals to specific social cognitive tasks when appraising the images. However, previous studies have shown that explicit instructions activate dorsal prefrontal areas, while the activation of the mirror neuron system and of context-representing regions such as the inferior frontal gyrus is identical in the instructed and in the passive exposure conditions (Iacoboni et al., 2005). Another possible and perhaps more likely explanation is that the context provided by the sequence of images in our task might have been too basic to differentiate sensitively between the relatively subtle deficits in BPD and healthy controls.

There were other limitations of the present study that may have affected our findings more generally. One is the relatively small size of the sample. Another is the fact that patients were medicated with antidepressants. These limitations have their origin in the difficulty in recruiting BPD individuals with acceptable comorbidity and medication profiles, in lack of resources to extend the study for longer recruiting times or areas, and in ethical constraints. For this reason, these limitations are shared with other studies in this area.

Together with previous studies, our data provide evidence of differences in the recruitment of cortical areas that are thought to contribute to encoding input of relevance to social cognition. There was evidence of increased activation of the mirror neuron system in BPD individuals, consistently with their putative role in the enhanced emotional contagion observed in BPD. However, this effect was selective, as did not extent to areas associated with elaboration of contextual information or representations of intentions, required to schematically organize percepts in the presence of some degree of ambiguity or complexity. The findings were consistent with notions in the clinical literature on BPD that emphasize not only the high emotional reactivity of these individuals but also the relatively low mentalization capacity in their encoding of interpersonal events.

Declarations of interest

None.

Acknowledgments

The authors declare no conflict of interest.

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