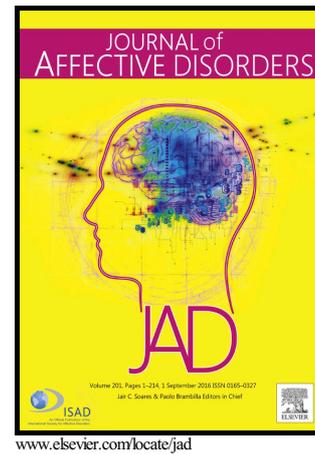


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**Amygdala and dlPFC abnormalities, with aberrant connectivity and habituation in response to emotional stimuli in females with BPD**

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## **Abstract**

### **BACKGROUND**

Little is known about the frontolimbic abnormalities thought to underlie borderline personality disorder (BPD). We endeavoured to study regional responses, as well as their connectivity and habituation during emotion processing.

### **METHODS**

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<sup>1</sup> equal contribution

14 BPD patients and 14 normal female controls (NC) controlled for menstrual phase underwent emotion-induction during an fMRI task using standardised images in a block design. We then performed psychophysiological interaction (PPI) analysis to investigate functional connectivity.

## RESULTS

BPD patients reported more disgust in questionnaires compared to controls. Relative to NC, they showed reduced left amygdala and increased dorsolateral prefrontal cortex (dlPFC) activation to all emotions collapsed versus neutral. Habituation of ventral striatal activity to repeated emotional stimuli was observed in controls but not in BPD. Finally, in the context of disgust (but not other emotions) versus neutral, BPD patients displayed enhanced left amygdala coupling with the dlPFC and ventral striatum.

## LIMITATIONS

Strict inclusion criteria reduced the sample size.

## CONCLUSIONS

In summary, BPD showed abnormal patterns of activation, habituation and connectivity in regions linked to emotion regulation. Amygdala deactivation may be mediated by abnormal top-down regulatory control from the dorsolateral prefrontal cortex. Aberrant emotion processing may play a unique role in the pathophysiology of BPD.

Keywords: borderline personality disorder; imaging; amygdala; disgust; functional connectivity; habituation

## INTRODUCTION

Borderline personality disorder (BPD) is defined by emotional dysregulation at its core and further comprises interpersonal difficulties, impulsivity, aggressive outbursts and dissociative symptoms. The disorder often involves patients experiencing profound distress, functional impairment, diminished quality of life<sup>1</sup> and is associated with high

suicidality and societal costs<sup>2</sup>. Further, it is characterised by its perceived lack of a legitimate neurobiological basis clinically<sup>3</sup>, making progress in understanding its pathophysiology particularly important. Whilst some progress understanding BPD has been made over recent years<sup>4</sup>, characterising its precise neurobiological correlates and mechanisms has been challenging. The majority of fMRI research to date in BPD has focused on abnormal limbic and amygdala responses to a range of emotive and aversive stimuli, auditory scripts and images<sup>5</sup>. Initial reports appeared consistent with the hypothesis of amygdala hyper-responsiveness to unpleasant stimuli<sup>6</sup>. Subsequent studies implicated a more dispersed complex of regions across the prefrontal cortex and limbic system together with a dual frontolimbic pathology model<sup>7</sup> suggesting a ‘failure of top down control’<sup>8</sup>. However, fMRI study findings and methods have not been consistent<sup>9</sup>, and whilst many studies reported limbic changes, several studies failed to replicate the initially reported amygdala hyperactivation. One meta-analysis<sup>9</sup> of 10 studies involving 225 subjects with BPD found an overall decrease amygdala activation whilst a more recent meta-analysis<sup>10</sup> conversely found increased amygdala activation in response to unpleasant stimuli. These meta-analyses have suggested key abnormalities in both frontal (including dorsolateral prefrontal cortex (dlPFC) and limbic (amygdala, hippocampus, anterior cingulate cortex (ACC)) areas consistent with overall frontolimbic dysfunction. Whilst such fMRI studies have explored different aversive emotions, behavioural studies have indicated specific deficits related to disgust, and this emotion has received limited attention. For instance, studies have shown BPD subjects make more errors recognising negative human facial emotions<sup>10</sup>, and this impairment may be more prominent to disgust compared to other negative emotions such as fear<sup>12</sup>. Recognising emotional cues in others may be an important skill for BPD subjects given its role in effective social functioning, disgust recognition deficits have been put forward as a potential explanatory mechanism for the problems subjects typically experience in developing and maintaining stable

relationships<sup>13</sup>. Focusing on one's own self, including one's own body lead to an increase both in self-disgust and self-harm urges in BPD<sup>14</sup>. Disgust processing errors have further been linked to suicidality, which is notably 50 times higher in BPD compared to the general population<sup>15</sup>. In a study of non-BPD, non-depressed patients, only errors recognising disgust and not other emotions was found to be significantly different between patients with and without previous suicide attempts<sup>16</sup>. Emerging evidence has suggested connectivity between frontolimbic brain regions could also be aberrant and responsive to Dialectical Behavioural Therapy<sup>17</sup>. Although frontolimbic dysfunction has been indicated to underlie BPD, the specific role of disgust, habituation and aberrant brain connectivity in its pathophysiology is less clear.

Here we investigate the neural correlates of emotional processing in BPD and further examine altered habituation which has received limited attention<sup>18</sup>. We compared BPD and matched normal controls in a functional MRI (fMRI) block design task comparing emotion-inducing images specifically with neutral images. We also included other positive and negatively valenced images for comparison purposes. In-line with recent meta-analysis findings<sup>9</sup>, we first hypothesized that BPD subjects would have lower amygdala activity to negative stimuli relative to neutral imagery compared to normal controls. Secondly, we hypothesized that disgust would be associated with reduced amygdala-prefrontal connectivity in BPD compared to normal controls consistent with impaired emotional regulation.

## PATIENTS & METHODS

### Participants

14 females with BPD and 14 female normal controls (NC) participated. Patients were recruited from the local personality disorder service and the controls via local advertisements. To control for known sex-specific differences related to processing emotion<sup>19,20</sup>, processing disgust<sup>21</sup> and effects of the menstrual cycle<sup>22</sup>, only females were recruited and wherever possible, scanned only during their follicular phase. All subjects were assessed and screened with strict criteria by a trained, experienced psychiatrist using structured diagnostic interview schedules (MINI International Neuropsychiatric Interview,<sup>23</sup>) and Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II<sup>24</sup>). Only subjects who fulfilled DSM IV-TR criteria for BPD were included. Those that met diagnostic criteria for other personality disorders were excluded. Further exclusion criteria included current major depressive disorder or lifetime history of any formally diagnosed psychotic illness or substance dependence identified in the MINI. Isolated subthreshold symptoms of a depressive, personality or psychotic disorder were allowed. Universal exclusion criteria also included those less than 18 years of age, MR-scanning incompatibility, and positive pre-scanning recreational urine drug screen. The local NHS research ethics committee approved this research (Cambridgeshire 4 Research Ethics Committee, NHS National Research Ethics Service, reference number: 09/H0305/10). Written informed consent was obtained from each participant. All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

**Measuring disgust and psychiatric indices**

Subjects completed standardised measures of depression (Beck Depression Inventory (BDI <sup>25</sup>); Hamilton Depression Rating Scale (HDRS <sup>26</sup>), anxiety (State and Trait Anxiety Inventory; STAI <sup>27</sup>), dissociation (Cambridge Depersonalisation Scale; CDS <sup>28</sup>) as well as the Borderline subscale of the Personality Assessment Inventory (PAI-BOR <sup>29</sup>) and body mass index (BMI). We assessed disgust using both general disgust (modified Disgust Scale Revised, m-DSR <sup>30</sup>) and self-disgust questionnaires (Self-disgust Scale (SDS) <sup>31</sup>).

**Emotion induction task**

We employed a block-design fMRI task using standardised intermixed emotion-inducing images from five emotional categories from the International Affective Picture System (disgust, anger, sad, happy and neutral) <sup>32</sup>. A Novel Image Series was presented before redisplaying the same pictures in a Repeated Image Series to assess for altered habituation (Figure 1). Repetitive emotional stimuli were presented to more closely mimic real-world experiences and maximise ecological validity. 50 trials of novel and repeated images were shown, both series consisting of a total of 10 unique images per emotional valence. Images were displayed in blocks of 5 sequential images of the same valence. Blocks of different emotional valences were randomised so that different emotion blocks were intermixed within the same series whilst this randomised order was kept constant across participants to control for effects of different duration latencies between first seeing an image and its repetition. For each trial, an emotion-inducing image was displayed for 6 seconds, before subjects were given 2 seconds to respond to a simple task as to whether the preceding picture was 'inside or outside' in order to assess task engagement. Then, a fixation cross was displayed for a further 2 seconds to provide an inter-trial interval before the next emotion-induction image was shown. The inter-stimulus-interval was not jittered. Trials were repeated as described until the experiment was complete.

## Neuroimaging Acquisition & Analysis

A 3T Siemens Magnetom TrioTim syngo MR B17 scanner was used with a 12-channel head coil using a tilted plane acquisition at the Wolfson Brain Imaging Centre in Cambridge. T2-weighted echo planar images (EPI) using interleaved slices were acquired. Parameters were TR=2000ms, TE=30ms, flip angle 78 degrees, matrix size 64x64, with 32 slices created with a slice thickness of 3mm (in-plane resolution 3mm x 3mm x 3mm). Analysis was performed using Statistical Parametric Mapping 8 (Wellcome Department of Cognitive Neurology, London, United Kingdom <http://www.fil.ion.ucl.ac.uk/spm>). Images were realigned and spatially normalised to standard Montreal Neurological Institute (MNI) space and smoothed with an 8mm full width at half-maximum Gaussian kernel. The first 6 volumes of each session were discarded to allow for T1 equilibration. Motion artefact was controlled for by including subject-specific realignment parameters in the general linear model.

Onsets and durations for displaying each emotion-inducing image were encoded for subjects at the first level. Second-level analysis was computed using a mixed measures 5x2 ANOVA with the within-subject factor of valence and between-subjects factor of Group. We first examined the effects of all emotional valences versus neutral and then specifically assessed disgust versus neutral. Three imaging analyses were conducted: (i) Whole-brain contrasts examining effects of group, emotional valence and habituation; (ii) Amygdala region of interest contrasts (iii) Amygdala functional connectivity. Whole-brain and ROI analyses were performed on only the Novel Presentations series of images. To assess for habituation, a series of images with Repeat Presentations was used and the number of times an image had been presented was encoded as a parametric modulation function at the first level. Age was used as covariate of no interest in the SPM model. To assess for neural

correlations of disgust and self-disgust, questionnaire scores were entered as a regressor into the SPM model.

For whole-brain contrasts, regions that survived FWE-correction at the cluster level at  $p < 0.05$  were considered significant. For *a priori* regions of interest, an amygdala mask was used from the Automated Anatomical Labelling atlas (AAL),<sup>33</sup>. For the ventral striatum, an 8mm sphere, the size of the smoothing kernel, was used centred on the nucleus accumbens of MNI coordinates -10 8 -4, as employed by previous studies<sup>34</sup>. Results were small-volume FWE-corrected, with  $P < 0.05$  considered significant. Functional connectivity using Psycho-Physiological Interaction (PPI) analysis was employed using a data-driven approach to map task-dependent functional connectivity between a seed region and the whole brain. A significant cluster here represented an interaction between a) the predictive relationship with the activity in a seed region and b) specific stimulus-related signal changes, meaning that the functional connectivity between the regions was dependent on the experimental stimulus. Hence PPI represents a measure of stimulus-dependent connectivity, describing responses in one region in terms of the interaction between responses in another region and a psychological process. We employed this PPI analytic approach for left amygdala seed. For the amygdala seed, we created a  $5\text{mm}^3$  sphere centered on the peak deactivation coordinates from our main ANOVA for disgust>neutral contrast (-18 -2 -28; Table 2). The blood-oxygen-level dependent time-course response (adjusted for the individual stimulus-specific effects) of our seed region was used as the physiological variable. Our 3 main contrasts (disgust>neutral; sad>neutral; and happy>neutral) were each used as psychological variables. We used these variables as regressors, along with the psychophysiological interaction term, in a single SPM model. We compared valence-dependent functional coupling between amygdala and regions identified in the main analysis (bilateral dlPFC and left ventral striatum) in BPD versus

normal controls, with small-volume corrected FWE  $P < 0.025$  (Bonferroni correction for multiple comparisons) considered significant.

## RESULTS

### Group characteristics and disgust scores

Detailed group characteristics detailing common comorbidities are listed in the Supplementary table. 10 of the subjects with BPD were taking psychotropic medication; The remaining 4 of the subjects with BPD were unmedicated. The BPD group mean age was slightly higher than the healthy group (36.3 versus 29.6 years;  $p = 0.038$ ). However in ANCOVA analyses, age did not have a significant effect as a covariate on BMI, BDI, HDRS, STAI state, m-DSR, SDS, or PAI-BOR indicating that any confounding effects were not significant. As typically found in previous studies<sup>35,36</sup>, BPD subjects scored higher than controls on measures of symptoms of depression, anxiety and depersonalisation. Figure 2 shows BPD subjects compared to controls scored significantly higher for self-reported disgust on the modified Disgust Scale-Revised (BPD: 15.32 [4.2]; NC: 8.94 [4.8]  $p = 0.003$ ) and particularly on the Self-disgust Scale (BPD 62.36 [10.4]; NC: 21.67 [7.4]  $p < 0.001$ ).

### Imaging outcomes

#### *Emotional valence versus neutral contrast*

We analysed the left and right Amygdala as *a priori* ROIs given our hypotheses. We showed that across all valences compared to neutral, there was significant decrease in activity in the left amygdala (left amygdala  $p(\text{FWE-corr}) < 0.015$ ; right amygdala  $p(\text{FWE-corr}) = 0.505$ ). Decreased activity was not significant in the comparison of disgust versus neutral.

We examined whole brain group differences for the contrast of all emotional valences versus neutral (Table 1). BPD subjects displayed higher left dlPFC activity across all valences relative to controls. The cluster localisation was confirmed to be in the dlPFC though was large in size and showed considerable extension medially (Figure 2a).

BPD subjects also showed lower activity across all valences in the temporal lobe and cerebellum. When disgust was compared to neutral, no clusters reached significance. Re-analysing data using BDI scores as a covariate of no interest did not alter the significant group differences. Disgust, self-disgust or dissociation scores did not correlate with brain activity.

#### *Emotional valence versus neutral: habituation effects*

Repeated presentation of emotive images was associated with reduced activity of striatum in normal controls but not in BPD. Whole-brain contrasts showed a well-circumscribed area (Figure 2C) in the left ventral striatum. Although this cluster did not survive correction for multiple comparisons ( $p=0.350$ ) at the whole-brain level, the ventral striatal region of interest analysis demonstrated significance in left ventral striatum in BPD compared to normal controls (peak MNI coordinates  $x=-8$   $y=14$   $z=-8$ ,  $k=40$  peak-level  $p(\text{FWE-corr})=0.001$ ). Hence, the reduced ventral striatum habituation seen in BPD compared to normal controls may reflect relatively low striatal initial activation to novel images which fails to further reduce in activity subsequently with repeated viewings.

#### *Functional connectivity*

Finally, we conducted PPI analyses to examine underlying frontolimbic connectivity in BPD compared to normal controls. In the context of disgust > neutral only, BPD showed increased functional connectivity between left amygdala and dlPFC (Brodmann areas 46

and 9 (left); peak coordinates, -34 40 10; small volume corrected (SVC) family-wise error (FWE),  $Z = 3.97$ ,  $p = 0.046$ ) compared to normal controls. In the same valence contrast, BPD also show increased functional connectivity between left amygdala and ventral striatum (validated anatomical masks<sup>33</sup>; peak coordinates, -16 10 -4; SVC FWE,  $Z = 3.47$ ,  $p = 0.018$ ). Self-report disgust scores did not significantly correlate with the strength of the connection between the left amygdala and dlPFC / ventral striatum. While disgust was associated with changes in connectivity between amygdala and regions implicated in emotional control, the other valences (sad>neutral, happy->neutral) did not elicit the same connectivity changes.

## DISCUSSION

In response to emotional versus neutral valences, we show that subjects with BPD relative to controls had a decrease in left amygdala and left ventral striatal activity and enhanced left dlPFC activity for all valence conditions combined. Our finding of decreased amygdala activity across all valences is consistent with the results of the previous meta-analysis by Ruocco et Al.<sup>9</sup> and contrasts with the meta-analysis of Schulze et Al. which found increased amygdala activity<sup>10</sup>. Divergent amygdala findings in different studies may relate to several study sample factors such as levels of dissociation and medication status. In a recent meta-regression analysis for example, medication-free samples demonstrated enhanced amygdala activation, whereas no such affect was found in medicated samples<sup>10</sup>.

We further show that normal controls had greater habituation of ventral striatal activation with repeated exposure to emotional valences, a phenomenon not observed in BPD subjects. Although we did not show a specific between-group effect of disgust, we demonstrated altered effect of enhanced functional connectivity between left amygdala and regions implicated in emotion regulation (dlPFC and ventral striatum) for disgust versus

neutral in BPD compared to normal controls. Further work is needed to determine whether such changes are specific to disgust compared to other emotions in BPD.

These findings of prefrontal hyperactivity and amygdala hypoactivity along with enhanced prefrontal-amygdala connectivity are consistent with abnormalities in top-down fronto-limbic control proposed in BPD<sup>4</sup>. We further replicate previous findings of elevated self-reported disgust in BPD<sup>37</sup>. Our neural findings emphasizing impaired fronto-limbic activity may explain the altered experience of disgust and reported abnormalities in over-attributing disgust<sup>38</sup>.

### *Amygdala*

The amygdala appears to be a crucial structure in BPD with both a decrease in structural volume<sup>39</sup> and aberrant functional activity<sup>9</sup> reported. A longitudinal study has reported treatment effects of dialectical behavioural therapy after a year of treatment in normalising aberrant amygdala activity<sup>40</sup>. However, the direction of amygdala activity to unpleasant stimuli in BPD fMRI studies has been inconsistent and may be related to methodological differences<sup>9</sup>. Some early evidence showed an increase in amygdala activity to aversive stimuli<sup>6,8,41-44</sup> whereas other studies have either not found a difference<sup>45,46</sup> or shown reduced activity<sup>47</sup>. More recently, a meta-analysis showed an overall reduction in amygdala activity to unpleasant stimuli<sup>9</sup> in line with our findings.

### *Dorsolateral prefrontal cortex*

Our findings of dlPFC hyperactivity in BPD in response to negative emotions is also supported by meta-analysis findings<sup>9</sup> showing similar between-group differences of increased left dlPFC unpleasant emotions in BPD compared to normal controls. Whilst the dlPFC is most well known for working memory and set shifting<sup>48</sup>, it plays an important role in upstream emotion control over multiple lower order regions of emotional regulation

<sup>49</sup>. The dlPFC is involved in higher order voluntary suppression of evaluation of emotion and voluntary suppression of sadness <sup>50</sup>. Further, repetitive TMS of the dlPFC has shown to affect early emotional attention in humans <sup>51</sup>. This is consistent with suggestions that increased dlPFC may result from increased effortful attempts to regulate emotions <sup>4</sup>, though these attempts to utilise cognitive strategies to modulate emotions are unfortunately largely ineffective in patients with a diagnosis of BPD <sup>46</sup>.

Our observation of an increase in dlPFC and amygdala functional connectivity in the contrast of disgust versus neutral in BPD compared to normal controls suggests a role for excessive or ineffective prefrontal emotional regulation. Other studies using different cognitive paradigms in BPD have also found dlPFC abnormalities. For example, in a PET study <sup>5</sup>, BPD showed bilateral increased dlPFC activity while recalling memories of abandonment. Alternatively, dissociative or functional symptoms which have greater prevalence in BPD <sup>52</sup> may play a role in left dlPFC activation. Other evidence for dlPFC disruption in BPD include observations of reduced prefrontal grey matter volumes in adolescent females with BPD <sup>53</sup> and evidence of focally reduced prefrontal neuronal viability found in patients in a pilot magnetic resonance spectroscopy study <sup>54</sup>. Prefrontal disruption is consistent with evidence of the heightened vulnerability of the left neocortex to early life stressors <sup>55-57</sup>, that have been implicated in BPD pathogenesis <sup>4</sup>. Similarly, cognitive deficits implicating the lateral prefrontal cortex have also been shown in BPD including deficits in working memory, visuo-constructive abilities and non-verbal executive function <sup>58</sup>.

Although BPD studies typically have high levels of coexisting depressive and anxiety symptoms, the dlPFC-amygdala findings differ in direction of activation and connectivity changes suggesting affective disorders are not a significant confound. In active major depressive disorder for example, Siegle et al. <sup>48</sup> found the inverse pattern of our findings showing reduced dlPFC and increased amygdala activity. Further, in extreme

early-life anxiety, connectivity between the central nucleus of the amygdala and the dlPFC has been found to be reduced, rather than increased as found in our study, in both monkeys and children with anxiety<sup>59</sup>. This would be expected if the study's main findings were independent of anxiety or depression-related comorbidity, though further study with larger sample sizes to improve mediation subanalyses is warranted.

Given the well-established role of the dlPFC in emotion regulation<sup>60,61</sup>, and our findings of enhanced dlPFC-amygdala coupling, we propose that the decrease in amygdala activity could represent abnormal suppression possibly mediated by the dlPFC. Such changes in connectivity could provide novel evidence to support proposed theories of frontolimbic dysfunction<sup>36</sup> in BPD.

#### *Ventral Striatum*

In BPD subjects compared to controls, we show reduced activity for initial viewings of images and reduced subsequent habituation to repeated images for all valences whilst only in the context of disgust is increased functional amygdala connectivity with the ventral striatum observed. Notably the decrease in habituation to repeated emotional valences in BPD subjects is likely related to the lack of activation to initial exposure. Previous BPD studies implicating the striatum and the caudate has shown both increased<sup>46,62</sup> as well as decreased<sup>5</sup> activity to negative emotions.

Several factors implicate the ventral striatum in BPD pathophysiology. The ventral striatum is commonly known for its role in reward learning, which may link to BPD given reports of heightened reinforcement sensitivity to both punishment and reward found in a sample of 100 BPD patients completing reward sensitivity questionnaires<sup>4</sup>. The ventral striatum is also thought to be involved in impulsivity, which is commonly observed in BPD<sup>63,4</sup>. Reduced ventral striatal grey matter volume has been linked to emotional dysregulation central to BPD. In a study of schizophrenic patients, the largest volume

difference in a voxel-based-morphometry study was found in the left ventral striatum of patients only with severe emotional dysregulation and not in patients without emotional dysregulation<sup>64</sup>. However, underlying mechanisms at the cellular level driving observed changes remain unclear from voxel-based morphometry studies<sup>65,66</sup>. Additionally, striatal abnormalities could play a role in intense outbursts of aggression prevalent in BPD, given its implication in intermittent explosive disorder<sup>67</sup>. In a positron emission tomography study of BPD subjects<sup>67</sup>, high levels of aggression and comorbid intermittent explosive disorder was associated with significantly lower striatal activity during an anger provocation computer game than normal controls. Further literature has linked the ventral striatum to altered expression of anger<sup>68</sup>.

### *Limitations*

Although the study sample size is relatively small, we employed strict exclusion criteria, and unlike previous studies, further controlled for menstrual cycle phase confounds. Further, clusters remained significant after covarying for depression scores. As our study was restricted to females, and known differences in disgust-processing have been found according to sex<sup>21</sup>, it is unclear how generalizable findings are to males. Further work with larger study sample sizes of both genders are needed, particularly to adequately power investigations of valence-specific effects and correlation analyses. Moreover, studies into the replicability of dlPFC findings are further needed to establish the role of this region as a potential biomarker for BPD emotional dysregulation.

### *Conclusion*

Our findings support recent evidence emphasizing the amygdala, ventral striatum and dlPFC as key regions in disturbed emotion regulation in BPD. We emphasize the role of top-down prefrontal-amygdala connectivity that appears to be disrupted during disgust

induction. Further understanding of pathophysiology will be critical for legitimising Borderline Personality Disorder as a condition with a strong neurobiological basis and developing novel therapies to target pathological disgust and frontolimbic dysfunction.

Conflict of interest: none

## References

- 1 IsHak WW, Elbau I, Ismail A, Delaloye S, Ha K, Bolotaulo NI, *et al.* Quality of life in borderline personality disorder. *Harv Rev Psychiatry* 2013; **21**: 138–50.
- 2 Wagner T, Fydrich T, Stiglmayr C, Marschall P, Salize H-J, Renneberg B, *et al.* Societal cost-of-illness in patients with borderline personality disorder one year before, during and after dialectical behavior therapy in routine outpatient care. *Behav Res Ther* 2014; **61C**: 12–22.
- 3 Dudas RB. What is it like to be diagnosed with bipolar illness, borderline personality disorder or another diagnosis with mood instability? *Br J Psychiatry* 2014; **204**: 178–9.
- 4 Leichsenring F, Leibling E, Kruse J, New AS, Leweke F. Borderline personality disorder. *Lancet* 2011; **377**. doi:10.1016/S0140-6736(10)61422-5.
- 5 Schmahl CG, Elzinga BM, Vermetten E, Sanislow C, McGlashan TH, Bremner JD. Neural correlates of memories of abandonment in women with and without borderline personality disorder. *Biol Psychiatry* 2003; **54**: 142–51.
- 6 Herpertz SC, Dietrich TM, Wenning B, Krings T, Erberich SG, Willmes K, *et al.* Evidence of abnormal amygdala functioning in borderline personality disorder: a functional MRI study. *Biol Psychiatry* 2001; **50**: 292–8.
- 7 Tebartz van Elst L, Hesslinger B, Thiel T, Geiger E, Haegele K, Lemieux L, *et al.* Frontolimbic brain abnormalities in patients with borderline personality disorder: a volumetric magnetic resonance imaging study. *Biol Psychiatry* 2003; **54**: 163–71.
- 8 Silbersweig D, Clarkin JF, Goldstein M, Kernberg OF, Tuescher O, Levy KN, *et al.* Failure of frontolimbic inhibitory function in the context of negative emotion in borderline personality disorder. *Am J ...* 2007; **164**: 1832–41.
- 9 Ruocco AC, Amirthavasagam S, Choi-Kain LW, McMMain SF. Neural correlates of negative emotionality in borderline personality disorder: an activation-likelihood-estimation meta-analysis. *Biol Psychiatry* 2013; **73**: 153–60.
- 10 Schulze L, Schmahl C, Niedtfeld I. Neural correlates of disturbed emotion processing in borderline personality disorder: a multimodal meta-analysis. *Biol*

- Psychiatry* 2016; **79**: 97–106.
- 11 Daros AR, Uliaszek AA, Ruocco AC. Perceptual biases in facial emotion recognition in borderline personality disorder. *Personal Disord Theory, Res Treat* 2014; **5**: 79.
  - 12 Nicol K, Pope M, Hall J. Facial emotion recognition in borderline personality: an association, with childhood experience. *Psychiatry Res* 2014; **218**: 256–8.
  - 13 Veague HB, Hooley JM. Enhanced sensitivity and response bias for male anger in women with borderline personality disorder. *Psychiatry Res* 2014; **215**: 687–93.
  - 14 Abdul-Hamid S, Denman C, Dudas RB. Self-relevant disgust and self-harm urges in patients with borderline personality disorder and depression: a pilot study with a newly designed psychological challenge. 2014.
  - 15 Association AP, Disorder APAWG on BP. *Practice guideline for the treatment of patients with borderline personality disorder*. American Psychiatric Pub, 2001.
  - 16 Richard-Devantoy S, Guillaume S, Olié E, Courtet P, Jollant F. Altered explicit recognition of facial disgust associated with predisposition to suicidal behavior but not depression. *J Affect Disord* 2013; **150**: 590–3.
  - 17 Schmitt R, Winter D, Niedtfeld I, Herpertz SC, Schmahl C. Effects of psychotherapy on neuronal correlates of reappraisal in female patients with borderline personality disorder. *Biol Psychiatry Cogn Neurosci Neuroimaging* 2016.
  - 18 Goodman M, Carpenter D, Tang CY, Goldstein KE, Avedon J, Fernandez N, *et al*. Dialectical behavior therapy alters emotion regulation and amygdala activity in patients with borderline personality disorder. *J Psychiatr Res* 2014; **57**: 108–16.
  - 19 Domes G, Schulze L, Böttger M, Grossmann A, Hauenstein K, Wirtz PH, *et al*. The neural correlates of sex differences in emotional reactivity and emotion regulation. *Hum Brain Mapp* 2010; **31**: 758–69.
  - 20 McRae K, Ochsner KN, Mauss IB, Gabrieli JJD, Gross JJ. Gender differences in emotion regulation: An fMRI study of cognitive reappraisal. *Gr Process Intergr Relations* 2008; **11**: 143–62.
  - 21 Schienle A, Schäfer A, Stark R, Walter B, Vaitl D. Gender differences in the processing of disgust- and fear-inducing pictures: an fMRI study. *Neuroreport* 2005; **16**: 277–80.
  - 22 Protopopescu X, Pan H, Altemus M, Tuescher O, Polanecsky M, McEwen B, *et al*. Orbitofrontal cortex activity related to emotional processing changes across the menstrual cycle. *Proc Natl Acad Sci U S A* 2005; **102**: 16060–5.
  - 23 Sheehan D V, Lecrubier Y, Harnett Sheehan K, Janavs J, Weiller E, Keskiner A, *et al*. The validity of the Mini International Neuropsychiatric Interview (MINI) according to the SCID-P and its reliability. *Eur Psychiatry* 1997; **12**: 232–41.
  - 24 First MB, Spitzer RL, Gibbon M, Williams JBW. The structured clinical interview for DSM-III-R personality disorders (SCID-II). Part I: Description. *J Pers Disord* 1995; **9**: 83–91.
  - 25 Beck AT, Steer RA, Ball R, Ranieri W. Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients. *J Pers Assess* 1996; **67**: 588–97.
  - 26 Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960; **23**: 56.

- 27 Spielberger CD. Manual for the State-Trait Anxiety Inventory STAI (form Y) ('self-evaluation questionnaire'). 1983.
- 28 Sierra M, Berrios GE. The Cambridge Depersonalisation Scale: a new instrument for the measurement of depersonalisation. *Psychiatry Res* 2000; **93**: 153–64.
- 29 Morey LC. Personality Assessment Inventory-Professional Manual. Florida, USA: Psychological Assessment Resources. 1991.
- 30 Olatunji BO, Williams NL, Tolin DF, Abramowitz JS, Sawchuk CN, Lohr JM, *et al.* The Disgust Scale: item analysis, factor structure, and suggestions for refinement. *Psychol Assess* 2007; **19**: 281.
- 31 Overton PG, Markland FE, Taggart HS, Bagshaw GL, Simpson J. Self-disgust mediates the relationship between dysfunctional cognitions and depressive symptomatology. *Emotion* 2008; **8**: 379.
- 32 Lang PJ, Bradley MM, Cuthbert BN. International affective picture system (IAPS): Technical manual and affective ratings. 1999.
- 33 Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, *et al.* Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage* 2002; **15**: 273–89.
- 34 Cools R, Clark L, Owen AM, Robbins TW. Defining the neural mechanisms of probabilistic reversal learning using event-related functional magnetic resonance imaging. *J Neurosci* 2002; **22**: 4563–7.
- 35 Mak ADP, Lam LCW. Neurocognitive profiles of people with borderline personality disorder. *Curr Opin Psychiatry* 2013; **26**: 90–6.
- 36 Lieb K, Zanarini MC, Schmahl C, Linehan MM, Bohus M. Borderline personality disorder. *Lancet* 2004; **364**: 453–61.
- 37 Schienle A, Haas-Krammer A, Schögl H, Kapfhammer H-P, Ille R. Altered state and trait disgust in borderline personality disorder. *J Nerv Ment Dis* 2013; **201**: 105–8.
- 38 Unoka Z, Fogd D, Füzy M, Csukly G. Misreading the facial signs: specific impairments and error patterns in recognition of facial emotions with negative valence in borderline personality disorder. *Psychiatry Res* 2011; **189**: 419–25.
- 39 Nunes PM, Wenzel A, Borges KT, Porto CR, Caminha RM, de Oliveira IR. Volumes of the Hippocampus and Amygdala in Patients With Borderline Personality Disorder: A Meta-Analysis. *J Pers Disord* 2009; **23**: 333–45.
- 40 Schnell K, Herpertz SC. Effects of dialectic-behavioral-therapy on the neural correlates of affective hyperarousal in borderline personality disorder. *J Psychiatr Res* 2007; **41**: 837–47.
- 41 Donegan NH, Sanislow CA, Blumberg HP, Fulbright RK, Lacadie C, Skudlarski P, *et al.* Amygdala hyperreactivity in borderline personality disorder: implications for emotional dysregulation. *Biol Psychiatry* 2003; **54**: 1284–93.
- 42 Koenigsberg HW, Fan J, Ochsner KN, Liu X, Guise KG, Pizzarello S, *et al.* Neural correlates of the use of psychological distancing to regulate responses to negative social cues: a study of patients with borderline personality disorder. *Biol Psychiatry* 2009; **66**: 854–63.

- 43 Minzenberg MJ, Fan J, New AS, Tang CY, Siever LJ. Fronto-limbic dysfunction in response to facial emotion in borderline personality disorder: an event-related fMRI study. *Psychiatry Res Neuroimaging* 2007; **155**: 231–43.
- 44 Beblo T, Driessen M, Mertens M, Wingenfeld K, Piefke M, Rullkoetter N, *et al.* Functional MRI correlates of the recall of unresolved life events in borderline personality disorder. *Psychol Med* 2006; **36**: 845–56.
- 45 Guitart-Masip M, Pascual JC, Carmona S, Hoekzema E, Bergé D, Pérez V, *et al.* Neural correlates of impaired emotional discrimination in borderline personality disorder: an fMRI study. *Prog Neuropsychopharmacol Biol Psychiatry* 2009; **33**: 1537–45.
- 46 Schulze L, Domes G, Krüger A, Berger C, Fleischer M, Prehn K, *et al.* Neuronal correlates of cognitive reappraisal in borderline patients with affective instability. *Biol Psychiatry* 2011; **69**: 564–73.
- 47 Smoski MJ, Salsman N, Wang L, Smith V, Lynch TR, Dager SR, *et al.* Functional imaging of emotion reactivity in opiate-dependent borderline personality disorder. *Personal Disord Theory, Res Treat* 2011; **2**: 230.
- 48 Siegle GJ, Thompson W, Carter CS, Steinhauer SR, Thase ME. Increased amygdala and decreased dorsolateral prefrontal BOLD responses in unipolar depression: related and independent features. *Biol Psychiatry* 2007; **61**: 198–209.
- 49 Hariri AR, Mattay VS, Tessitore A, Fera F, Weinberger DR. Neocortical modulation of the amygdala response to fearful stimuli. *Biol Psychiatry* 2003; **53**: 494–501.
- 50 Lévesque J, Eugène F, Joannette Y, Paquette V, Mensour B, Beaudoin G, *et al.* Neural circuitry underlying voluntary suppression of sadness. *Biol Psychiatry* 2003; **53**: 502–10.
- 51 Zwanzger P, Steinberg C, Rehbein MA, Bröckelmann A-K, Dobel C, Zavorotnyy M, *et al.* Inhibitory repetitive Transcranial Magnetic Stimulation (rTMS) of the dorsolateral prefrontal cortex modulates early affective processing. *Neuroimage* 2014.
- 52 Vermetten E, Spiegel D. Trauma and dissociation: implications for borderline personality disorder. *Curr Psychiatry Rep* 2014; **16**. doi:10.1007/s11920-013-0434-8.
- 53 Brunner R, Henze R, Parzer P, Kramer J, Feigl N, Lutz K, *et al.* Reduced prefrontal and orbitofrontal gray matter in female adolescents with borderline personality disorder: is it disorder specific? *Neuroimage* 2010; **49**: 114–20.
- 54 van Elst LT, Thiel T, Hesslinger B, Lieb K, Bohus M, Hennig J, *et al.* Subtle prefrontal neuropathology in a pilot magnetic resonance spectroscopy study in patients with borderline personality disorder. *J Neuropsychiatry Clin Neurosci* 2001; **13**: 511–4.
- 55 Teicher MH, Andersen SL, Polcari A, Anderson CM, Navalta CP, Kim DM. The neurobiological consequences of early stress and childhood maltreatment. *Neurosci Biobehav Rev* 2003; **27**: 33–44.
- 56 Teicher MH, Andersen SL, Polcari A, Anderson CM, Navalta CP, Kim DM. The neurobiological consequences of early stress and childhood maltreatment. *Neurosci Biobehav Rev* 2003; **27**: 33–44.
- 57 Arnsten AFT. Stress signalling pathways that impair prefrontal cortex structure and

- function. *Nat Rev Neurosci* 2009; **10**: 410–22.
- 58 Dinn WM, Harris CL, Aycicegi A, Greene PB, Kirkley SM, Reilly C. Neurocognitive function in borderline personality disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 2004; **28**: 329–41.
- 59 Birn RM, Shackman a J, Oler J a, Williams LE, McFarlin DR, Rogers GM, *et al.* Extreme early-life anxiety is associated with an evolutionarily conserved reduction in the strength of intrinsic functional connectivity between the dorsolateral prefrontal cortex and the central nucleus of the amygdala. *Mol Psychiatry* 2014; **19**: 853.
- 60 Banks SJ, Eddy KT, Angstadt M, Nathan PJ, Phan KL. Amygdala–frontal connectivity during emotion regulation. *Soc Cogn Affect Neurosci* 2007; **2**: 303–12.
- 61 Stein JL, Wiedholz LM, Bassett DS, Weinberger DR, Zink CF, Mattay VS, *et al.* A validated network of effective amygdala connectivity. *Neuroimage* 2007; **36**: 736–45.
- 62 Niedtfeld I, Schulze L, Kirsch P, Herpertz SC, Bohus M, Schmahl C. Affect regulation and pain in borderline personality disorder: a possible link to the understanding of self-injury. *Biol Psychiatry* 2010; **68**: 383–91.
- 63 Mole T, Irvine M, Worbe Y, Collins P, Mitchell S, Bolton S, *et al.* *Impulsivity in disorders of food and drug misuse.* , 2014 (<http://europepmc.org/abstract/med/25118940>).
- 64 Stegmayer K, Horn H, Federspiel A, Razavi N, Bracht T, Laimböck K, *et al.* Ventral striatum gray matter density reduction in patients with schizophrenia and psychotic emotional dysregulation. *NeuroImage Clin* 2014; **4**: 232–9.
- 65 Mole T, MacIver K, Sluming V. Specific brain morphometric changes in spinal cord injury with and without neuropathic pain. *NeuroImage Clin* 2014; **5**: 28–35.
- 66 Mechelli A, Price CJ, Friston KJ, Ashburner J. Voxel-based morphometry of the human brain: methods and applications. *Curr Med Imaging Rev* 2005; **1**: 105–13.
- 67 Mercedes Perez-Rodriguez M, Hazlett EA, Rich EL, Ripoll LH, Weiner DM, Spence N, *et al.* Striatal activity in borderline personality disorder with comorbid intermittent explosive disorder: sex differences. *J Psychiatr Res* 2012; **46**: 797–804.
- 68 Calder AJ, Keane J, Lawrence AD, Manes F. Impaired recognition of anger following damage to the ventral striatum. *Brain* 2004; **127**: 1958–69.

**Figure 1. Emotion-induction fMRI task.** Standardized emotion inducing images are shown to the subject initially as a series of novel presentations and subsequently with repeat presentations to assess for habituation effects.

**Figure 2. Aberrant emotional processing in BPD compared to controls.** (A) Left dlPFC hyperactivation in BPD relative to controls across all valences collapsed versus neutral.

Cluster remains significant corrected for multiple comparisons (FWE). (B) Bilateral amygdala *a priori* region-of-interests showing deactivation in BPD relative to controls across all valences. Results were significant collapsed across all valences in SVC analysis. (C) The left ventral striatum showed reduced activation on repeated viewing of all valenced images (whole-brain uncorrected cluster displayed). (D) Significantly elevated disgust in BPD from self-report questionnaires compared to controls. (E) Amygdala Hyperconnectivity in the context of disgust to areas involved in emotion regulation and impulsivity in Borderline Personality Disorder. Seed region based on left amygdala found to be hypoactive in BPD relative to controls for all emotional valences, including disgust. Aberrant connectivity not found for other emotional valences. Psycho-physiological interaction analysis from disgust versus neutral contrast. Clusters significant after small-volume-correction and adjustment for Family-Wise Error  $p < 0.05$ . Clusters shown in (i) dIPFC (ii) ventral striatum (iii) vmPFC. dIPFC, dorsolateral prefrontal cortex; vmPFC ventromedial prefrontal cortex; BPD, Borderline Personality Disorder Group; NC, normal control group; m-DSR, modified Disgust Scale-Revised; SDS, self-disgust scale; dIPFC, dorsolateral prefrontal cortex; VS, ventral striatum;

**Table 1. Whole-brain group effects collapsed across all valences for novel stimuli presentations**

Activity	Region	Laterality	MNI coordinates			z score	p (FWE-corr)
			x	y	z		
↑	dorsolateral prefrontal cortex	left	-16	38	30	5.32	<0.001
↓	cerebellum	right	-26	-48	-42	7.14	<0.001
	middle temporal gyrus	left	-56	-2	-24	6.13	<0.001

**Table 2. Functional connectivity during disgust versus neutral in BPD compared to normal controls with amygdala seed region**

Seed Region	Connectivity	Region	MNI coordinates			Z-score	p (FWE-corr)
			x	y	z		
Left Amygdala	↑	dIPFC (left & right)	-34	42	8	4.14	0.017
	↑	ventral striatum (left)	-16	10	-4	3.47	0.01

FWE-corr: Family-wise error corrected

dIPFC: dorsolateral prefrontal cortex

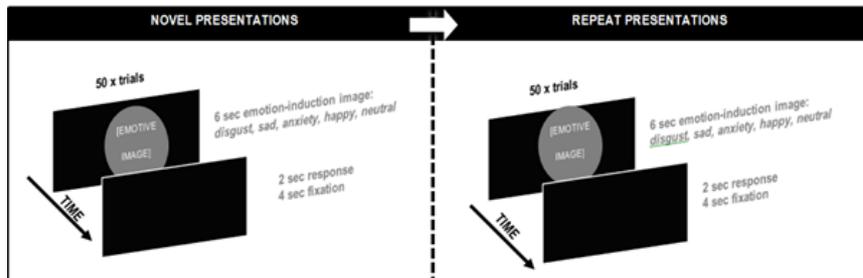
vmPFC: ventromedial prefrontal cortex

Z: Z-connectivity score

coordinates are peak values in MNI space

## Highlights

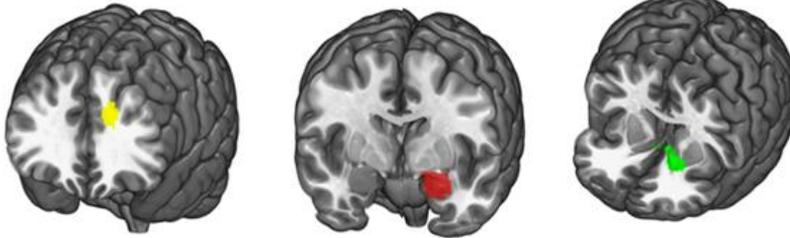
- The neurobiological basis for Borderline personality disorder is unclear
- Responding to emotional stimuli results in aberrant brain activity patterns
- Abnormal functional connectivity and habituation is implicated
- Abnormal amygdala and prefrontal functioning is specifically implicated



Accepted

## All-valence effects

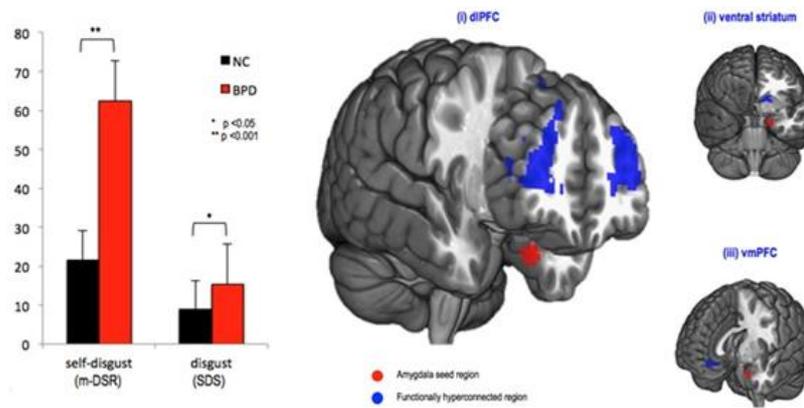
- (A) whole-brain dlPFC hyperactivation (B) amygdala hypoactivation\* (C) reduced habituation in VS\* with repeated emotion induction



\*region-of-interest analysis

## Disgust-specific abnormalities

- (D) Elevated disgust self-report scores (E) Disgust-specific amygdala-prefrontal / striatal hyperconnectivity\*



Accepted