Neural correlates of fears of abandonment and rejection in borderline personality disorder
Romaniuk, Liana; Pope, Merrick; Nicol, Katie; Steele, John; Hall, Jeremy

Published in:
Wellcome Open Research

DOI:
10.12688/wellcomeopenres.10331.1

Publication date:
2016

Citation for published version (APA):
Neural correlates of fears of abandonment and rejection in borderline personality disorder [version 1; referees: awaiting peer review]

Liana Romaniuk 1, Merrick Pope 1, Katie Nicol 1, Douglas Steele 2, Jeremy Hall 1,3,4

1Division of Psychiatry, University of Edinburgh, Edinburgh, UK
2Medical Research Institute, University of Dundee, Dundee, UK
3Neuroscience and Mental Health Research Institute, Cardiff University, Cardiff, UK
4MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Cardiff, UK

Abstract

Background: Borderline personality disorder (BPD) is a prevalent and disabling psychiatric condition commonly associated with early life adversity. Social difficulties are a prominent symptom of BPD, particularly a fear of abandonment and rejection. There has recently been a growing interest in the neural basis of these social symptoms and their relationship to early experience. Methods: In the current study, we examined social brain function and learning in BPD using functional MRI. Participants with BPD (n=20) and healthy controls (n=16) completed a computerized parametric social exclusion task (the “Cyberball” task). Brain activation was compared between groups and related to social symptom status and experiences of childhood trauma. Additional analyses were conducted using a reinforcement learning model treating social inclusion as a rewarding event. Results: Participants with BPD demonstrated a group effect of decreased right temporoparietal junction (TPJ) activation (p < 0.013, FWE-corrected). Increased fear of abandonment in BPD was associated with reduced inclusion-related activation of the inferior frontal gyrus (p = 0.003, FWE-corrected). Across all participants, TPJ inclusion-related activation was modified by prior experience of childhood physical neglect (p < 0.001, FWE-corrected). Reinforcement learning modelling revealed decreased midbrain responses to social inclusion in BPD participants (p = 0.028, FWE-corrected within midbrain mask), with decreased anticipatory midbrain activation in anticipation of social inclusion specifically associated with fears of abandonment (p = 0.019, FWE-corrected within a midbrain mask).

Conclusions: The findings demonstrate alterations in social brain function and social reinforcement learning in BPD, which are influenced by both early life experience and symptom status.
Corresponding author: Liana Romaniuk (lianaromaniuk@gmail.com)

How to cite this article: Romaniuk L, Pope M, Nicol K et al. Neural correlates of fears of abandonment and rejection in borderline personality disorder [version 1; referees: awaiting peer review] Wellcome Open Research 2016, 1:33 (doi: 10.12688/wellcomeopenres.10331.1)

Copyright: © 2016 Romaniuk L et al. This is an open access article distributed under the terms of the Creative Commons Attribution Licence, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Grant information: This work was supported by the Wellcome Trust [DEFINE, 100202/Z/12/Z]; a Scottish Senior Clinical Fellowship [SCD/10]; the MRC Centre [G0800509]; and the Waterloo Foundation [Changing Minds programme]. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: No competing interests were disclosed.

First published: 29 Dec 2016, 1:33 (doi: 10.12688/wellcomeopenres.10331.1)
Introduction

Borderline personality disorder (BPD) is a common and serious disorder associated with significant impact on the individual, their families and a wide range of healthcare providers1-3. Social difficulties are a core feature of BPD, and include marked fears of abandonment and social rejection4-6. Indeed these factors underlying their characteristically disturbed relationships have been proposed to be a phenotype of this personality disorder6. Both genetic and early environmental factors have been shown to contribute risk for developing BPD symptoms7,8,9, with evidence that early environmental factors, such as childhood adversity10, play a particularly prominent role in the development of BPD11 and interpersonal symptoms in particular12,13.

Fear of abandonment is one of the core symptoms of BPD recognized in both Diagnostic and Statistical Manual of Mental Disorder (DSM)-5 and International Statistical Classification of Diseases and Related Health Problems (ICD)-10. Fearing abandonment is one of the most stable features of the disorder, and is associated with negative core beliefs14,15 and an increased propensity for self-injurious behavior16-18. The central nature of this symptom is further confirmed by formal testing, in which people with BPD show heightened sensitivity to rejection and abandonment in questionnaire measures19, and increased psychophysiological reactions to scripts relating to abandonment20.

The marked fear of abandonment seen in people with BPD is reflected in the disorganised attachment patterns observed in these patients21-23. Abnormalities in the development of secure attachment patterns are considered to underlie the development of persistent fear of rejection seen in people with BPD24,25. The development of stable attachment relationships requires the experience-dependent maturation of specific brain circuitry mediating key aspects of social function and learning, such as mentalizing,26-28. Such regions include the superior temporal cortex, temporoparietal junction (TPJ), and insula and inferior frontal gyrus (IFG)29. Theoretical analyses of BPD have suggested that altered social learning during development, potentially secondary to childhood adversity, may lead to the emergence of key symptoms of BPD, such as fear of abandonment30,31.

Within BPD, several imaging studies have assessed the processing and regulation of emotion, self-injury, cognitive disturbance and impulsivity (see reviews 26,27). However, there has been an increasing interest in imaging the neurobiological mediating interpersonal difficulties. The behavioural and neural correlates of social rejection and social learning can be studied experimentally using computer games28,29. A commonly applied task is the “Cyberball” game, in which the participant takes part in a computerised ball-throwing game with two on-screen figures, where the degree to which the participant is included or excluded from the game is systematically varied29. Imaging studies using the Cyberball task have revealed a network of brain regions that are sensitive to the degree of inclusion and exclusion, including frontal and temporal brain regions implicated in social cognition30-33. It has also been shown that social inclusion events produce reward learning signals in a range of brain regions, including the inferior frontal cortex and posterior temporal areas that are known to be involved in social behavior34,35.

In the current study, we built on previous studies of BPD using the Cyberball task31,32,33,40. Ruocco et al. demonstrated that people with BPD demonstrate increased medial prefrontal cortex (PFC) activation during social exclusion34. Using functional MRI (fMRI), Domsalla and colleagues found that people with BPD exhibited generalised hyperactivation of dorsal medial PFC, anterior cingulate, precuneus and superior/inferior parietal lobules, and that this activity was not modulated by social inclusion, as was seen in controls41. We extended this work by examining the relationship between Cyberball brain activation and (a) BPD symptoms of social difficulty, named fears of abandonment and unstable relationships; and (b) reported early life adversity. We also analysed the results in terms of social reward learning models and demonstrate altered reward learning in BPD consistent with previous models of the disorder42. We hypothesised that within people with BPD, social inclusion-evoked brain activation would demonstrate associations with previous childhood adversity, and their current interpersonal symptoms. These associations would likely be demonstrated in areas mediating mentalizing, namely the superior temporal cortex, insula and IFG.

Methods and materials

Participants

A total of 20 people with borderline personality disorder (BPD) were recruited from outpatient and support services from around Edinburgh, Scotland. Diagnoses were confirmed using the Structured Clinical Interview for DSM-IV (SCID-II; http://www.scid4.org/). Current symptoms were assessed using the Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD)43. Adverse childhood events were assessed using the Childhood Trauma Questionnaire (CTQ)44. In total, 15 BPD participants were receiving antidepressant medication and 12 were taking antipsychotic medication. Demographic details are given in Table 1.

Experimental task

Participants performed the Cyberball social exclusion task20 during fMRI, adapted from a previous implementation by Kumar et al. 200933. The task involves playing “catch” with two computer-controlled players, during which the participant can be systematically included or excluded from the game. We used this task as it assesses neural responses to social exclusion, is known to activate a range of social brain regions34, and is amenable to reinforcement learning modelling35. The task was modified such that inclusion was varied parametrically over four levels: 0%, 33%, 66% and 100%, achieved by arranging the task into blocks of nine throws, respectively involving zero, one, two or three throws to the participant (Supplementary material; Supplementary Figure 1). Here, 100% inclusion means the degree to which the participant was included.
was equal to that of the other two players, with each receiving three throws per nine-throw block. Mean block duration was 24s (in part dependent on participants’ reaction times), with onsets denoted by the appearance of the cartoon figures following rest, and offsets by the conclusion of the final throw animation. Blocks were randomized, and interleaved with 13s rest blocks. Within blocks, throwing events were jittered to permit event disambiguation for reinforcement learning analysis. Reaction times were analysed within a repeated measures ANOVA (within-subjects: inclusion level; between-subjects: group). Response bias, that is the propensity to favour one computer player over the other, was also assessed (Supplementary methodology; Supplementary Results).

Neuroimaging

Full neuroimaging methods are provided in the Supplementary methodology. In summary, fMRI data was acquired at 3T, with TR 1560ms, 347 volumes, resolution 3.4 × 3.4 × 5mm. A T1 structural image was acquired with resolution 1mm isotropic. Data were preprocessed and analysed using SPM8 (Wellcome Department of Imaging Neuroscience, London, England; http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) within MathWorks Matlab R2014a (http://www.mathworks.com), including its normalisation to MNI space, and smoothing using an 8mm FWHM Gaussian kernel.

At the first-level, each level of inclusion was modelled using separate regressors. Motion parameters were included as nuisance regressors. T-contrasts were generated for each inclusion level > rest, and taken into a random-effects second-level full factorial design matrix, modelling inclusion and diagnostic group. Both the main effects and the interaction were evaluated.

The relationships between current social symptoms and fMRI response to increasing inclusion were examined within a second level multiple regression of the first-level parametric contrast of increasing inclusion (100% > 66% > 33% > 0%), by the ZAN-BPD Total Disturbed Relationships sub-score items. Focusing on social interaction, this comprises items six (frantic efforts to avoid real or imagined abandonment; Z6) and nine (unstable and intense interpersonal relationships; Z9). It has been theorized that several characteristics of borderline psychopathology, especially those concerning interpersonal relationships, are secondary to changes in social cognition and motivation.

Table 1. Study participant demographics. CTQ, Childhood Trauma Questionnaire; ZAN-BPD, Zanarini Rating Scale for Borderline Personality Disorder; PTSD, post-traumatic stress disorder; OCD, obsessive compulsive disorder.

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Borderline personality disorder (n = 20)</th>
<th>Healthy volunteers (n = 16)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Mean [SD])</td>
<td>35.8 (8.6)</td>
<td>34.8 (9.6)</td>
<td>0.97</td>
</tr>
<tr>
<td>IQ (Mean [SD])</td>
<td>114.8 (7.9)</td>
<td>114.5 (6.0)</td>
<td>0.58</td>
</tr>
<tr>
<td>Gender (F:M)</td>
<td>17:3</td>
<td>13:3</td>
<td>0.76</td>
</tr>
<tr>
<td>CTQ (Mean [SD]) Range 1–5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical abuse</td>
<td>2.51 (1.45)</td>
<td>1.09 (0.24)</td>
<td>0.002</td>
</tr>
<tr>
<td>Physical neglect</td>
<td>2.14 (1.11)</td>
<td>1.28 (0.32)</td>
<td>0.010</td>
</tr>
<tr>
<td>Emotional abuse</td>
<td>3.79 (1.10)</td>
<td>1.25 (0.41)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Emotional neglect</td>
<td>3.35 (1.36)</td>
<td>1.54 (0.77)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sexual abuse</td>
<td>3.14 (1.74)</td>
<td>1.28 (0.32)</td>
<td>0.001</td>
</tr>
<tr>
<td>ZAN-BPD Total</td>
<td>13.7 (6.7)</td>
<td>0.0 (0.0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medication</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipsychotics only</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Antidepressants only</td>
<td>5</td>
<td>25</td>
</tr>
<tr>
<td>Both</td>
<td>10</td>
<td>50</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comorbid Diagnoses</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>17</td>
<td>85</td>
</tr>
<tr>
<td>Depression</td>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>Anxiety</td>
<td>6</td>
<td>30</td>
</tr>
<tr>
<td>Eating disorder</td>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>PTSD</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>OCD</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Bipolar type 2</td>
<td>1</td>
<td>5</td>
</tr>
</tbody>
</table>
in self-other representations. Any assessment of one’s relationships with others implicitly involves the consideration of self, and could therefore be modulated by its disturbance, outside the boundaries of any one particular personality disorder. Therefore, we also included ZAN-BPD item four (identity disturbance: markedly and persistently unstable self-image or sense of self; Z4) in this single symptom regression analysis. The impact of past childhood adversity on fMRI responses to increasing inclusion were also assessed within a separate second level multiple regression incorporating the subscales of the CTQ (physical/emotional abuse/neglect, and sexual abuse).

We also adopted a reinforcement learning approach, examining how those with BPD learn to anticipate the rewarding outcome of social inclusion. Reinforcement learning models describe mathematically the learning processes that occur during conditioning and reward learning and closely relates to the observed changes in dopaminergic neuron firing seen in animals. Previous studies have demonstrated that reinforcement learning approaches are applicable to social learning tasks, including the Cyberball task. A temporal difference reinforcement learning model represented the task as an instance of classical conditioning, where those moments when the ball was received by the participant being modelled as a rewarding unconditioned stimulus (outcome), and moments when the ball was held by the computer-controlled characters as a conditioned stimulus (anticipation). fMRI regressors describing the anticipatory and outcome phases of each ball throw were modulated by a parametric regressor modelling the prediction error at these moments, using MathWorks Matlab R2014a. The outcome phase represents trial-by-trial responses to inclusion (reward=1) and exclusion (reward=0), whereas anticipation captures learning regarding potential inclusion (see Supplementary methodology for more information). As well as group comparisons, patients’ contrasts were also regressed by the three social symptoms (Z4, Z6, Z9).

For all fMRI analyses, a voxel-wise threshold of p < 0.001 was applied, and only those regions additionally achieving a cluster-wise FWE-corrected significance of p < 0.05 were reported. As temporal difference models have been shown to provide a good account for midbrain activation during reward learning, the reinforcement learning analyses were corrected within an anatomically-defined mask comprising the substantia nigra and ventral tegmental area (Supplementary methodology).

**Results**

**Behaviour and psychopathology**

There were no performance differences between the groups as assessed by reaction times across the task (F(1,34) = 0.21; p = 0.65), indicating matched engagement with the task (Supplementary Figure 2). Participants with BPD had significantly greater Zanarini and CTQ scores than controls, as expected (Table 1).

**Main effect of inclusion on brain activation**

Examining the main effect of increasing inclusion on brain activation across the groups revealed robust activation of several brain regions known to be engaged during social cognition, including the IFG, inferior parietal lobule/TPJ, anterior cingulate cortex, caudate and thalamus (Supplementary Figure 3).

**Main effect of group on brain activation**

Across the task as a whole, participants with BPD showed lower activation of the right TPJ and left middle occipital cortex bilaterally (Figure 1).

![Figure 1. Controls > BPD across all levels of inclusion.](image-url)

The behavioural personality disorder (BPD) group showed diminished temporoparietal junction activation across the Cyberball task as a whole (Table 2). Activation map displayed at a voxel-wise uncorrected threshold of p < 0.001; however, only clusters achieving a FWE-corrected significance of p < 0.05 are reported. Bar chart demonstrates R temporoparietal junction activation (TPJ) at each level of inclusion for both groups.
levels of reported childhood physical neglect were associated with a decreased inclusion response within bilateral superior temporal cortex, and middle anterior cingulate cortex (Table 2; Figure 2). These effects remained significant even when restricted to the BPD group only (p < 0.002). No effects were seen for the other CTQ subscales or total score.

### Table 2. Functional imaging activation statistics.

Regions showing significant relationships between the inclusion response, and either Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD) or Childhood Trauma Questionnaire (CTQ) measures, reported in MNI space. The latter two analyses concerning fear of abandonment and physical neglect were performed within the behavioural personality disorder (BPD) group only.

<table>
<thead>
<tr>
<th>Region</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>kE</th>
<th>Peak Z score</th>
<th>P value (cluster extent FWE-corrected)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls &gt; BPD across all inclusion levels</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L middle occipital cortex</td>
<td>-30</td>
<td>-91</td>
<td>10</td>
<td>201</td>
<td>4.52</td>
<td>0.008</td>
</tr>
<tr>
<td>R temporoparietal junction</td>
<td>51</td>
<td>-37</td>
<td>13</td>
<td>128</td>
<td>4.84</td>
<td>0.037</td>
</tr>
<tr>
<td>Fear of abandonment (Zanarini 6) x decreased inclusion activation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R inferior frontal cortex</td>
<td>39</td>
<td>29</td>
<td>10</td>
<td>3729</td>
<td>5.32</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sub-peaks within this cluster</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L postcentral cortex</td>
<td>-30</td>
<td>-34</td>
<td>52</td>
<td>3729</td>
<td>5.32</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>L superior temporal cortex</td>
<td>-48</td>
<td>-28</td>
<td>-2</td>
<td>450</td>
<td>4.31</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Physical neglect (CTQ) x decreased inclusion activation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L temporoparietal junction</td>
<td>-39</td>
<td>-22</td>
<td>19</td>
<td>450</td>
<td>4.31</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>R middle cingulate cortex</td>
<td>6</td>
<td>-10</td>
<td>46</td>
<td>195</td>
<td>4.31</td>
<td>0.002</td>
</tr>
<tr>
<td>R insula cortex</td>
<td>45</td>
<td>-4</td>
<td>16</td>
<td>346</td>
<td>4.27</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Figure 2. Associations between brain responses to inclusion, fear of abandonment and past physical neglect. Red indicates areas having a negative association between Zanarini item 6 (fear of abandonment) and the response to increasing inclusion. This is restricted to the behavioural personality disorder (BPD) group, as controls had no variance for any Zanarini item. Blue indicates areas having a negative relationship between Childhood Trauma Questionnaire (CTQ) physical neglect, and increasing inclusion. This incorporates both groups. (a) Sagittal slice at MNI X = 39, highlighting R inferior frontal gyrus and insula. (b) Sagittal slice at MNI X = -48, highlighting L superior temporal and temporoparietal junction structures. Maps are displayed at an uncorrected voxel-wise threshold of p < 0.001; however, only clusters with a FWE-corrected significance p < 0.05 are reported.
Relationship of social symptoms in BPD to brain activation

Analysis of the effect of social symptoms of BPD on brain activation was restricted to the BPD group, due to a floor effect for these symptoms in the control group. This analysis revealed that increasing fear of abandonment was associated with a reduced response to inclusion within the right IFG, and left postcentral gyrus within the BPD group (Table 2; Figure 2).

Temporal difference modelling of inclusion events as rewarding

We next used temporal difference modelling to examine neural responses to individual events of inclusion and exclusion, with inclusion events treated as rewarding. Compared to controls, participants with BPD showed significantly less activation in the midbrain during trials on which they were included, suggesting that their experience of inclusion was not imbued with the same salient or rewarding character as that felt by controls (Figure 3a; MNI -9 -13 -14; Z = 3.26; p = 0.028, FWE-corrected within the midbrain mask). There was no association between midbrain outcome responses and social symptom status, suggesting that decreased midbrain response to inclusion may represent a stable feature of the condition. We further examined brain activation during the anticipation phase of each trial. In participants with BPD, increasing fear of abandonment was associated with reduced midbrain activation, suggesting a diminished ability to learn to anticipate inclusion (Figure 3b; MNI 6 -13 -14; Z = 3.55; p = 0.019, FWE-corrected within the midbrain mask). There were no associations between midbrain activation and childhood adversity.

Correlation with medication and depressive symptoms

Neither depressive symptoms nor medication status correlated with activation of the R IFG, TPJ or midbrain (Supplementary results; Supplementary Figure 4).

Discussion

In healthy individuals, social inclusion in the Cyberball task activated a network of brain regions including the inferior frontal gyrus (IFG) and temporoparietal junction (TPJ). Participants with BPD demonstrated a number of differences in brain activation during the Cyberball task. Firstly, participants with BPD showed reduced activation of the TPJ across all levels of inclusion. Secondly, individuals with BPD showed altered activation of the right IFG in relation to a key symptom of the disorder - fear of abandonment. Thirdly, TPJ, insula and anterior cingulate cortex (ACC) responses in both groups were modified by prior experiences of childhood physical neglect. Finally, participants with BPD showed a decreased reward response to social inclusion in the midbrain, and decreased anticipatory midbrain responses to social inclusion in relation to symptoms of fear of abandonment. Overall these results demonstrate sustained alterations in the TPJ and midbrain in BPD with additional modulation of RIFG function in relation to fear of abandonment.

Figure 3. Altered midbrain responses in the BPD group. (a) Prediction error signal, controls > behavioural personality disorder (BPD), displayed at p < 0.001 uncorrected. (b) The relationship between the R inferior frontal gyrus (IFG) response to increasing inclusion, the anticipatory response of midbrain to inclusion, and fear of abandonment.
to the key symptom of fear of abandonment. Differences in TPJ function were in part related to adverse childhood experience.

There was a main effect of group within the right TPJ, with participants with BPD demonstrating reduced activation. The difference was not attributable to behavioural performance, which was matched across groups; however there was no significant task x group interaction in this region, meaning this could not be firmly attributed to altered responses to inclusion per se. Notably these findings are consistent with those reported in a previous study of BPD. However, the TPJ is known to play a key role in social behavior and has been implicated in social reward learning. The roles of posterior temporal regions in social function are complex, but are believed to sub-serve core components of reciprocal social interaction, imitation and relating self to others. The TPJ has in particular been implicated in considering the internal states of others, and in learning social rules about how much to trust another individual. Individuals with BPD can have difficulty in developing trust in relationships and show a tendency to rate others as untrustworthy on formal testing. They have also demonstrated reduced activation in nearby posterior superior temporal structures during a cognitive empathy and attribution of emotional empathy tasks. Decreased activation of TPJ in individuals with BPD is thus likely to reflect an impaired ability to predict and trust other’s social intentions.

We also found that in BPD activation of the right IFG, a core component of the social brain network, was related to the symptom of fear of abandonment. The IFG is known in both primates and humans to contain neurons that are involved in social learning and show activation which “mirrors” responses seen in others, in particular encoding the intention of the other’s action and attribution of emotional empathy tasks. Decreased activation of TPJ in individuals with BPD is thus likely to reflect an impaired ability to predict and trust other’s social intentions.

We additionally sought to determine whether experience of childhood adversity might contribute to the development of altered social brain responses across both groups. Regression of childhood trauma questionnaire scores against brain activation during the Cyberball task revealed that greater experiences of physical neglect during childhood were associated with reduced responses to social inclusion within left TPJ, right insula, and ACC. Physical neglect represents a definitive breakdown of normal reciprocal social interactions during childhood. These results therefore support the view that impaired nurturing from caregivers during childhood alters one’s understanding of the likely outcomes of social interactions. As the negative relationship was also seen in insula, this suggests that physical neglect also impacts on the normal development of one’s interoceptive sensations in the context of social interactions. Correlations with brain activation during the Cyberball task were not seen for the other four CTQ measures. This could however be due to a lack of power to detect an effect in this sample or be because of resistance – conscious or otherwise - to the recall of physical or sexual abuse.

The IFG and TPJ have both been implicated in mediating the brain’s responses to the rewarding nature of social inclusion and interaction. Specifically these regions show temporal patterns of activation during social learning, which are consistent with those seen to a range of other rewarding stimuli. The underlying source of these reward-related brain signals is believed to be the firing of dopaminergic neurons in midbrain regions, which have been shown to be phasically responsive to reward learning in animal models and in human imaging studies. Here we examined the response of the midbrain to social inclusion events in BPD by modelling inclinations events as rewarding. This analysis showed that participants with BPD showed decreased midbrain activation to the reward of social inclusion than control participants, suggesting that people with BPD have a diminution of positive reward responses to social experience. In addition, participants with BPD with greater fear of abandonment also showed decreased activation of the midbrain in response to the anticipation of social inclusion. Phasic dopamine release has been argued to be more representative of the expectation-outcome mismatch i.e. reward prediction error, rather than simple hedonistic reward itself. It has been suggested that the pervasive rejection felt by people with BPD – even when being fully included – may be due to people with BPD biasing their perceptions to conform to their expectations, in which case, a dopaminergic “prediction error” signal is unlikely to be generated. This apparent selective blindness to inclusion in people with BPD is additionally supported by evidence from EEG studies. Indeed it seems that only during conditions of extreme over-inclusion do people with BPD report reduced negative emotions during social interaction.

A number of important limitations to the current study should be noted. Firstly, we did not directly measure the participants’ subjective experience of the different levels of social inclusion during the task. Previous behavioural studies have shown that individuals with BPD show greater feelings of exclusion during the Cyberball task. However we chose not to directly assess responses to the changing task contingencies in the present study, as doing so would necessarily interrupt the flow of the task and alert the participants to the covert changes in the degree of inclusion, whilst post-task analysis would be confounded by the differing degrees of inclusion/exclusion present across the task. Secondly, participants with BPD in the current study had a number of comorbid conditions and many were on some form of medication. However, we chose to include participants with typical outpatient presentations of BPD, increasing the generalisability of our findings. Notably, we did not identify any consistent relationship between the differences in social brain activation seen in the study and the most common comorbid conditions, such as depression, or treatment with either antidepressant or antipsychotic medications. Thirdly, our results appear to differ from those of Kumar et al., who also adopted a reinforcement learning approach to Cyberball data, but did not find TD-associated...
midbrain activation. This could be because their data was acquired at 1.5T or because the randomized nature of our inclusion blocks induced more abrupt violations of expectation. Our studies are qualitatively comparable, although we introduced a degree of jitter in considering the anticipation of inclusion, whereas their implementation was fixed, albeit on a similar time scale.

Conclusions
The current findings illuminate the neural basis of key social symptoms in borderline personality disorder and their relationship to developmental experience. We show that participants with BPD have differential activation of brain regions mediating social interaction, including the TPJ and midbrain. TPJ activation was also found to be related to childhood physical neglect. Furthermore, individuals with BPD experiencing a high fear of abandonment had altered brain responses during social learning in key brain regions mediating social interactions and reward, including the IFG. These results provide a framework for the further translational modelling of disrupted social reward learning in BPD. Future therapies for BPD may aim to reprogram this altered circuitry by training people with these symptoms to learn that social interaction can have sustained positive outcomes.

Data availability
Functional and structural MRI data, together with behavioral log files, demographics, medication and psychopathology data are available through OpenfMRI (accession number, ds000214; https://openfmri.org/dataset/ds000214/).

Consent
All participants provided written informed consent before taking part. Written informed consent for publication of the participants’ anonymised details and data were obtained from the participants.

Author contributions
JH conceived the study. LR, DS and JH designed the experiment. LR, MP, KN and JH carried out the research. LR and JH prepared the first draft of the manuscript. All authors were involved in the revision of the draft manuscript and have agreed to the final content.

Competing interests
No competing interests were disclosed.

Grant information
This work was supported by the Wellcome Trust [DEFINE, 100202/Z/12/Z]; a Scottish Senior Clinical Fellowship [SCD/10]; the MRC Centre [G0800509]; and the Waterloo Foundation [Changing Minds programme].

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgements
We thank Stephen Giles for data curation and analysis support. We thank all the participants for their efforts in taking part.

Supplementary material
Supplementary methodology: Additional information is provided regarding the Cyberball task; behaviour, neuroimaging and reinforcement learning analyses.

Click here to access the data.

Supplementary results: Additional results regarding response bias, depressive symptoms and medication.

Click here to access the data.

Supplementary Figure 1: The Cyberball task. The two computer-controlled players are represented by figures on either side of the screen, and the participant by a hand near the lower centre. The trial starts with the ball being held by either one of the computer players, or the participant: here an inclusion throw is illustrated, where the participant receives the ball. After a jittered delay, the throwing of the ball is animated. When held by the participant, they select a computer player to throw to with a button press. The random jitter is adjusted in part to accommodate the participant’s reaction time from the previous trial. For the reinforcement learning analysis, the conditioned stimulus (CS) occurred halfway between the moment of the ball being caught and thrown again by another player; the unconditioned stimulus (US) was the time the ball was caught by another player (exclusion), or the participant (inclusion).

Click here to access the data.

Supplementary Figure 2: Behavioural results. Mean reaction times for BPD (blue) and healthy controls (green) across inclusion levels. Error bars indicate ±1 SE. 

Click here to access the data.

Supplementary Figure 3: BOLD responses to increasing social inclusion. Activation maps are thresholded at p < 0.05 FWE-corrected. Table displayed activation peaks. Resel size: 16.4 16.0 16.4, count: 279.

Click here to access the data.
Supplementary Figure 4: Impact of medication status. Scatterplots displaying the relationships between medication status and three results described in the paper. Participants are divided according to whether they are unmedicated, taking antidepressants, taking antipsychotics, or taking both. (a) Right inferior frontal cortex response to increasing inclusion versus Zanarini fear of abandonment. Data is shown for those with BPD only. (b) CTQ physical abuse versus left superior temporal cortex response to increasing inclusion. Both those with BPD and controls are shown. (c) Midbrain anticipation of inclusion versus Zanarini fear of abandonment. This too incorporates only those with BPD.

Click here to access the data.

References


