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Atypical processing of social anticipation and feedback in borderline personality disorder

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ABSTRACT

Background-: Borderline personality disorder (BPD) is characterized by maladaptive social functioning, and widespread negativity biases. The neural underpinnings of these impairments remain elusive. We thus tested whether BPD patients show atypical neural activity when processing social (compared to non-social) anticipation, feedback, and particularly, how they relate to each other.

Methods-: We acquired functional MRI data from 21 BPD women and 24 matched healthy controls (HCs) while they performed a task in which cues and feedbacks were either social (neutral faces for cues; happy or angry faces for positive and negative feedbacks, respectively) or non-social (dollar sign; winning or losing money for positive and negative feedbacks, respectively). This task allowed for the analysis of social anticipatory cues, performance-based feedback, and their interaction.

Results-: Compared to HCs, BPD patients expressed increased activation in the superior temporal sulcus during the processing of social cues, consistent with elevated salience associated with an upcoming social event. BPD patients also showed reduced activation in the amygdala while processing evaluative social feedback. Importantly, perigenual anterior cingulate cortex (pgACC) activity during the presentation of the social cue correlated with reduced amygdala activity during the presentation of the negative social feedback in the BPD patients.

Conclusions-: These neuroimaging results clarify how BPD patients express altered responses to different types of social stimuli (i.e. social anticipatory cues and evaluative feedback) and uncover an atypical relationship between frontolimbic regions (pgACC-amygdala) over the time span of a social interaction. These findings may help to explain why BPD patients suffer from pervasive difficulties adapting their behavior in the context of interpersonal relationships and should be considered while designing better-targeted interventions.

1. INTRODUCTION

Borderline personality disorder (BPD) is a serious illness affecting up to 6% of the general population (Lenzenweger et al., 2007; Grant et al., 2008). BPD is characterized by interpersonal dysfunction, including a severe fear of abandonment, marked impulsivity, negative self-evaluations, and emotional dysregulation (American Psychiatric Association 2013).

According to prominent theories of BPD, particularly Linehan's biosocial theory (Carpenter and Trull, 2013; Crowell et al., 2009; Linehan, 1993), disrupted attachment profiles, alongside heightened trait emotional sensitivity, and a propensity to experience high levels of negative affect are all relevant to the development of BPD psychopathology. Together, these components result in an inability to learn appropriate emotional regulation strategies resulting in the development and use of dysregulated behaviors to manage and reduce negative

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affect, particularly during social interactions. Compared to healthy controls (HCs), BPD patients have been shown to be especially sensitive to social rejection (e.g. (Bungert et al., 2015)), express an attentional bias toward negative emotional information (BPD adults: (Domes et al., 2006; Bertsch et al., 2013); adolescents with BPD/high levels of BPD features: (Jovev et al., 2012; Von Ceumern-Lindenstjerna et al., 2009)), integrate undesirable social feedback (based on their character traits) to a greater degree (Korn et al., 2016; Van Schie et al., 2019; Fineberg et al., 2018), and experience more intense negative (and reduced positive) affective responses as a result of social feedback (Van Schie et al., 2019; Jeung et al., 2018). Additionally, these patients generally perceive the faces of others to be untrustworthy, which is consistent with heightened threat anticipation from social contexts (Miano et al., 2013; Fertuck et al., 2013; Nicol et al., 2014), even anticipating potential threat *before* a confrontive social interaction (Deckers et al., 2015). It is thus by no means surprising that these patients experience difficulties in varied social contexts and yet the interpersonal/social dysfunction component of BPD tends to be the most difficult and unsatisfactorily treated (Lis and Bohus, 2013). Unfortunately, relatively few studies have investigated social interactions in BPD, especially from a neuroimaging perspective. Moreover, accounting for how the processing of a social interaction unfolds, from anticipation to the actual experience of a social event, would likely help to develop more targeted therapeutic approaches and thus provide increased quality of life (e.g. improving social integration; (Lis and Bohus, 2013; Minzenberg, 2017)).

Thus far, the majority of fMRI studies on negative emotionality in BPD have focused on the (mostly passive) processing of (unpleasant) emotional stimuli, including mainly faces, but also scenes (e.g. (Scherpiet et al., 2014; Enzi et al., 2013; Nicol et al., 2015); for meta-analyses see: (Schulze et al., 2016; Ruocco et al., 2013; Schulze et al., 2018)). These studies have highlighted atypical activations and functional interplay between brain areas subserving top-down emotional processes, including the medial prefrontal cortex (mPFC) and anterior cingulate cortex (ACC) (Scherpiet et al., 2014; Schulze et al., 2016; Chechko et al., 2016), and limbic areas, especially the amygdala (Schulze et al., 2016; Ruocco et al., 2013; Ruocco and Carcone, 2016). Specifically, compared to HCs, the processing of negative emotional stimuli generally resulted in hyper-reactivity of the amygdala/limbic system, which is thought to be associated with subjectively more intense experiences of negative emotions in these patients (Schulze et al., 2016; Ruocco et al., 2013; Ruocco and Carcone, 2016; Mauchnik and Schmahl, 2010). Furthermore, frontolimbic networks were found to be differentially recruited even during the anticipation of negative emotional stimuli (i.e. during the presentation of a cue predictive of an upcoming negative event; (Scherpiet et al., 2014; Enzi et al., 2013)), which may catalyze faulty emotional adjustment in these patients (Scherpiet et al., 2014; Ruocco et al., 2013). While reactions to social/emotional stimuli are controlled by these abovementioned top-down processes (Stevens et al., 2011), it is not yet clear whether and how differential anticipation influences the processing of subsequent social stimuli (particularly for performance-based socially evaluative feedback, see below).

Generally, throughout the day we are confronted with a variety of emotional/social information, whose underlying meaning must be interpreted as a function of the ongoing context. When a negative (e.g., angry) face is seen following one's erroneous behavior, the face takes on a double meaning: it expresses a negative emotion, and it also conveys a negative social evaluation. Additionally, if that social evaluation is preceded by an anticipatory signal (e.g. someone warning you about an imminent judgment), we are able to emotionally "prepare" ourselves to receive that signal. Given that BPD patients are likely always expecting negative feedback, especially in the context of a social interaction, they might not only express altered recruitment of limbic brain regions in response to social feedback, but the degree of this difference might also be modulated by the anticipatory activity of top-down mechanisms from frontal regions (e.g. mPFC, dACC, and pgACC; (Stevens et al., 2011)).

The aim of the present study was to determine the processing of social (compared to non-social) cues and feedbacks in patients with BPD compared to HCs. We utilized fMRI and a modified incentive delay task (Knutson et al., 2001; Spreckelmeyer et al., 2009) in which anticipatory cues and subsequent performance-based feedbacks (i.e. winning and losing outcomes) were either social (neutral faces for cues; happy or angry faces for positive and negative feedbacks, respectively) or non-social (dollar sign; winning or losing money for positive and negative feedbacks, respectively). Because of the way this task was designed, participants rapidly (and efficiently) learned that a cue (i.e. neutral face in the social condition, or dollar sign in the non-social condition) would be followed by feedback directly corresponding to their performance (i.e. performance-based feedback). For example, in the social condition, the neutral face was followed either by a smiling, happy face whenever participants responded "properly" (i.e. fast enough), or by an angry face whenever they were too slow. This design allowed us to test our three main hypotheses. The first hypothesis (H1) was that BPD patients, compared to HCs, would exhibit differential neural activation mainly of frontal regions (e.g. mPFC, and ACC; similar to (Scherpiet et al., 2014; Enzi et al., 2013)) in response to social compared to non-social anticipatory cues (i.e. neutral faces compared to monetary cues). The second hypothesis (H2) was that BPD patients would express differential limbic reactivity to evaluative social feedback (e.g. angry faces), particularly in the amygdala (e.g. (Schulze et al., 2016; Ruocco et al., 2013)). Finally, because BPD patients have been shown to express atypical processing across frontolimbic networks (see above), our third, and main, hypothesis (H3) was that how the processing of an anticipatory cue (by frontal regions) relates to the subsequent social feedback (amygdala) may be a key feature of BPD. Specifically, given the pervasive negative bias of these patients, this relationship should be critically involved during negative social evaluations (e.g. hypo-regulatory anticipatory frontal activity should lead to a hyper-reactive limbic response to negative social feedback).

2. Methods and materials

2.1. Participants

Twenty-one female BPD patients, age 21–38 (M = =27.43, SD = 5.22), who met the DSM-5 criteria for BPD and 24 female HCs participants, age 19–36 (M = =24.71, SD = 5.50), without any lifetime psychiatric diagnoses were included. We recruited BPD outpatients from a specialized ambulatory service in Geneva (Switzerland), and the HCs were contacted by advertisements.

All participants were first screened for inclusion criteria and then assessed by a trained psychologist and a psychiatrist (see Supplementary Material). BPD diagnosis was established through medical records and standardized measures (Diagnostic Interview for Genetic Studies [DIGS]; (Nurnberger et al., 1994)) and the SCID-II (Screening Interview for Axis II; (First et al., 1997)) BPD part (see Table 1). Similar to our previously published article (Olié et al., 2018), we created an index of "medication load" for each patient in order to test for the effects of medication on significantly activated brain regions (see Supplementary Material). We also assessed BPD symptom severity using the Borderline-Symptom-List (i.e. the BSL-23; (Bohus et al., 2007; Nicastro et al., 2016)) rated within one week before the scanning session. Level of depression was assessed by the Montgomery and Asberg Depression Rating Scale (MADRS; (Montgomery and Asberg, 1979)) and the 13 item Beck Depression Inventory II (BDI-II; (Beck et al., 1961)). History of childhood maltreatment was assessed by Childhood Trauma Questionnaire (CTQ) French version (Bernstein et al., 1994) (All questionnaires are reported in Table 2). For more details about clinical assessment, please see the Supplementary Material.

The study was approved by the Ethics committee of the Geneva

Table 1
Comorbidity and medication list for the BPD group ($N = 21$).

	N	percentage (%)
Comorbidities		
Major Depressive Episode	18	85.71
Currently Depressed	8	38.10
Bipolar Disorder	3	14.29
Anxiety Disorder	13	61.90
Social Phobia	10	47.62
Agoraphobia	3	14.29
PTSD	1	4.76
Panic Disorder	3	14.29
GAD	3	14.29
ADHD	7	33.33
Eating disorder	2	9.52
Lifetime history of at least one suicide attempt	11	52.38
Medications		
Antidepressants	13	61.90
SSRI	11	52.38
SSNRI	2	9.52
Antipsychotics	5	23.81
Benzodiazepines	3	14.29
Methylphenidate	3	14.29

ADHD = attention deficit hyperactivity disorder; BPD = borderline personality disorder; GAD = generalized anxiety disorder; PTSD = post traumatic stress disorder; SSNRI = selective serotonin and norepinephrine reuptake inhibitors.

University Hospitals. Each participant provided written informed consent.

2.2. Experimental design and tasks

The task was designed to be a modified version of the monetary and social incentive delay task (see (Spreckelmeyer et al., 2009; Knutson et al., 2000)) with two different conditions, social and non-social, and two distinct time points of interest in each trial, cues and feedbacks. Each trial began with a cue indicating the type of trial (social or non-social) followed by a fixation cross (Fig. 1). Participants were then asked to rapidly press a button as soon as a target appeared on the screen. If they pressed the button while the target was still on the screen, they were presented with a winning feedback and if not, they were presented with a losing feedback. The delay between cue onset and feedback onset was jittered between 3350 ms and 5100 ms. Target presentation time depended on the outcome of the participant's previous trial of the same condition. The presentation time of the target for the first trial was 400 ms and if the participant responded during the allotted time, 25 ms was subtracted from the next presentation time of the same condition, if the participants responded after the allotted time, 25 ms was added. This allowed for an online adaptation of the target's presentation time for each participant, to reach an overall performance of approximately 60% winning. Any trial where a participant pressed the button before the onset of the target was considered a miss, and no adaptation of presentation time was performed.

The task was modeled with 20 mini-blocks of 4 consecutive trials of the same condition (e.g. 4 consecutive social trials followed by 4 non-social trials) resulting in 40 of each social and non-social conditions. Mini-blocks were employed in order to reduce attentional load required for the participants, as well as to avoid any "spillover" effects from one condition to the next (e.g. in BPD patients, (a et al., 2012)). These mini-blocks were counter-balanced and delivered in a pseudorandom order (with never more than 2 mini-blocks of the same type in a row). For the social condition, we used 40 individual faces (20 female) with neutral (for the cues), happy and angry expressions (for the feedbacks) from the Karolinska Directed Emotional Faces database (Lundqvist et al., 1998). To familiarize the participants with the task and to remove any effects of learning, a practice session was performed before the fMRI session, outside the scanner, using faces which were not included in the fMRI experiment. To ensure that all participants understood the task fully, we questioned them about the meaning of the feedback following each trial.

2.3. MRI data acquisition and analysis

Functional images were acquired using a multiplexed EPI sequence (Feinberg et al., 2010) with repetition time (TR) = 650 ms, echo time (TE) = 30 ms, flip angle = 50°, 36 slices, 64 × 64 pixels, voxel size = 3 × 3 × 3 mm. The multiband acceleration factor was 4, and parallel acquisition technique (PAT) was not used. Structural images were acquired with a T1 weighted 3D sequence (MPRAGE, TR/inversion time/TE = 1900/900/2.27 ms, flip angle = 9°, PAT factor = 2, matrix size = 256 × 256 × 192, voxel size = 1 × 1 × 1 mm).

All fMRI data analyses, including image preprocessing and analyses, were performed using SPM8 software (http://www.fil.ion.ucl.ac.uk/spm) implemented in Matlab R2012b. During preprocessing, the functional volumes were first realigned to the mean image, normalized using the EPI template provided with the SPM toolbox, and finally smoothed with an 8 mm^3 Gaussian kernel. To account for any residual movement artefacts after realignment, we used the Artefact Detection Toolbox (ART; http://web.mit.edu/swg/software.htm; see Supplementary Material for thresholds employed). In addition to utilizing the ART toolbox, we also visualized a portion of the images from each participant at each analysis step in order to ensure the quality of the data.

Statistical analyses were performed on a voxel-wise basis across the whole-brain. Using an event-related approach, individual events were convolved with a standard synthetic hemodynamic response function (HRF). Six individual regressors represented the main event types. For the cues: social and non-social cues; for the feedback: social win outcome, social lose outcome, non-social win outcome, non-social lose outcome. Events corresponding to feedback for erroneous responses (i.e. key presses before target onset), the key presses themselves, motion parameters, and outlier scans identified by ART were modeled as

Table 2
Questionnaire results.

		BPD			HC			Comparative statistics		
Questionnaire	Subscale	Mean	SD	N	Mean	SD	N	t	df	p
BDI	Total	24.33	7.82	21	1.63	1.91	24	12.98	22.08	< 0.001
BSL-23	Total	41.10	14.08	21	1.58	2.38	24	12.70	21.00	< 0.001
CTQ[a]	Emotional Abuse	14.10	4.85	21	6.42	3.11	24	6.23	33.22	< 0.001
	Physical Abuse	7.19	3.27	21	5.33	0.64	24	2.56	21.33	0.018
	Sexual Abuse	8.00	5.00	21	5.50	2.06	24	2.14	25.91	0.042
	Emotional Neglect	14.67	4.40	21	7.50	3.04	24	6.27	34.89	< 0.001
	Physical Neglect	8.05	3.44	21	6.13	1.92	24	2.27	30.39	0.030
SCID-II	Total (BPD part)	7.24	1.22	21	–	–	–	–	–	–

BDI = beck depression inventory; BPD = borderline personality disorder; BSL-23 = borderline symptom checklist-23; HC = healthy controls; SCID-II = structured clinical interview for DSM disorders; SD = standard deviation.

[a] Each question of the CTQ is marked on a 5-point Likert scale from 1 ("never true") to 5 ("always true") and so each subscale ranges from 5 to 25.

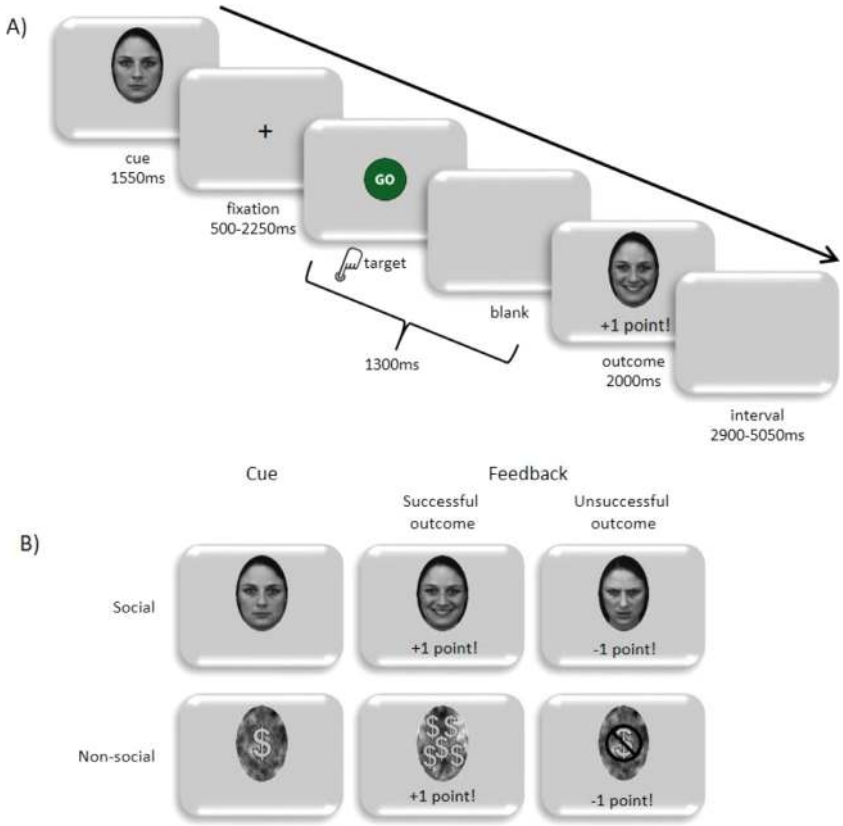

Fig.. 1. Schematic depiction of the social reward task (A) and example stimuli (B).

nuisance regressors. A high-pass filter with 128 s was also applied. The relevant first-level contrasts were built and used during the second-level analyses.

To answer our three hypotheses, we modelled three separate second-level analyses. Model 1 aimed to test H1, by determining the differences between HCs and BPD patients for the processing of social cues versus non-social cues. Hence, the corresponding linear contrasts for each participant were entered into a 2 × 2 full factorial model with one within-subjects factor 'Social Condition' (social, non-social) and one between-subjects factor 'Group' (HC, BPD). Model 2 was conducted to test H2, by determining the differences between the groups when processing social feedback. The corresponding linear contrasts were entered into a separate 2 × 2 × 2 full factorial model with two within-subject factors 'Social Condition' (social, non-social) and 'Reward Outcome' (win, lose), and one between-subjects factor 'Group' (HC, BPD). As we expected to find group differences in the frontal brain in Model 1 (i.e. anticipatory social cue processing) and the amygdala in Model 2 (i.e. socially evaluative feedback processing), we utilized a region-of-interest (ROI) analysis approach using the WFU PickAtlas toolbox for SPM (Maldjian et al., 2004; Maldjian et al., 2003). Specifically, we created one mask of the frontal lobe (used to test H1 in Model 1) and a second mask of the bilateral amygdala (used to test H2 in Model 2), both of which were from the Talairach Daemon database. Follow-up exploratory full brain analyses were then conducted (see below for thresholding information).

Model 3 was created *ad hoc* in order to test H3 following the outcome of the first two models. In particular, we speculated that there would be group differences between frontal regions at the time-point of the cues (as tested by Model 1) and the limbic processing during the following negative social feedback (as tested by Model 2). However, as we did find group differences in the amygdala for Model 2, but not in the frontal cortex for Model 1 (see the Results section), we ran a seed-based analysis, using the amygdala feedback-related activity for the negative social (compared to non-social) component of Model 2 as the predictor and testing against potential relationship with cue-evoked signal at a voxel-wise level within Model 1. Specifically, the beta estimates for both groups from the bilateral amygdala ROI for the negative social feedback (i.e. social loss > non-social loss) were extracted from Model 2 and entered as a covariate into an independent samples *t*-test using the specific contrast social > non-social cues (see the SPM design matrix in Supplementary Figure S1). We then tested for the effects of the amygdala covariate in each group separately and compared the differences between the groups. Please note that, although this analysis shares many properties with seed-based connectivity approaches (e.g., psycho-physiological interactions), it differs from the latter by testing the interaction between different epochs (anticipatory cue versus feedback). Hence, results should not be necessarily interpreted in terms of online communication between brain areas, but rather in terms of delayed influence, wherein the anticipatory activity in the highlighted regions explains the subsequent amygdala response during negative social feedback (versus non-social). Finally, for sake of completeness, we repeated the seed-based analysis using instead the betas extracted from the positive social feedback (i.e. social win > non-social win). The results from this model (i.e. Model 4) are described in the supplementary materials.

ROI analyses were conducted using the pipeline implemented in the WFU PickAtlas toolbox with a familywise error (FWE) correction of $p < .05$. Follow-up whole-brain activations are reported at a significance level of $p < .001$ and a $k > 88$, which corresponds to $p < .05$ corrected, based on the most stringent of three Monte Carlo Simulations (one for each fMRI Model) conducted using the toolbox RestPlus (Song et al., 2011). Employing this combination of height and cluster correction has been shown to lead to reliable results, with an acceptable tradeoff between type-I and type-II errors (Cox et al., 2017). In order to illustrate the relative activation of the different brain regions, mean beta estimates were extracted from 8 mm spheres surrounding the activation

peak.

2.4. Psychometric and statistical analysis

To test the differences in the self-report questionnaires between the two groups, independent *t*-tests were performed. Additionally, where appropriate, analyses of variances/co-variances (ANOVA/ANCOVA) were used to compare the differences between reaction times and check for effects of medication load as well as comorbid disorders (see Supplementary Materials for results). Finally, we used Spearman's correlation to help understand how childhood trauma, a main BPD risk factor, might relate to amygdala activity in the BPD patients (following the outcome of Model 2, see Results). We chose the amygdala because this region has not only consistently been shown to express dysfunctional activation in a variety of BPD neuroimaging studies (see Introduction section), but childhood trauma (measured via the CTQ) has also been shown to correlate with amygdala responsiveness to negatively valenced faces in HC subjects (Dannlowski et al., 2013). We used the software package IBM SPSS 22 (SPSS Inc., Chicago, IL) with a significance threshold set to $a = = 0.05$.

3. Results

3.1. Behavioral results

3.1.1. Reaction times

The ANOVA comparing reaction times for responses to the target presentation did not show any significant main effects nor an interaction between the two groups for the social and non-social conditions (mean (SD) ms for HCs: social = 250.14 (35.16), non-social = 246.02 (31.43); BPD patients: social = 257.75 (43.00), non-social = 258.30 (51.46); all $p > .29$), suggesting that BPD patients did not differ from the HCs.

3.1.2. Neuroimaging results

3.1.2.1. Model 1: interaction social condition by group for cues. To test H1, that BPD patients expressed dysfunctional recruitment of frontal brain regions in response to social (compared to non-social) cues, we directly compared both groups by computing the 2-way interaction 'Social Condition' (social, non-social cues) by 'Group' (HC, BPD) within the frontal lobe mask. This ROI analysis did not reveal any significantly activated voxels. When seeking effects across the whole brain, we found that the BPD patients (compared to HCs) hyperactivated the right superior temporal sulcus (STS) for social versus non-social cues (Fig. 2; Supplementary Table S1). Raw beta estimates extracted from the peak of this region (i.e. Fig. 2B) showed that BPD patients expressed greater STS activation to social cues compared to the HCs, a difference not observed for the non-social cues. It should be noted that estimates extracted from the STS are often below the baseline (i.e. negative), most likely due to the high activations in this region during resting state (e.g. (Mitchell et al., 2002; Peelen M et al., 2010)). There were no significantly activated voxels in the opposite contrast.

3.1.2.2. Model 2: interaction social condition by group for feedback. To test H2, that BPD patients would show impaired amygdala response to social feedback, we conducted ROI analyses (i.e. frontal lobe and amygdala masks) using the 2-way interaction 'Group' x 'Social Condition' for the feedback analysis. BPD patients expressed a blunted response of the bilateral amygdala compared to the HCs for the social versus non-social feedback contrast (Fig. 3). Extracting the raw beta estimates from the peak (Fig. 3B) showed that the HCs, compared to the BPDs, expressed a larger difference in activity for the social compared to the non-social conditions. When seeking effects across the whole brain we found no suprathreshold results (see Supplementary Table S2 for full voxel-wise analysis). Interestingly, exploratory analyses showed that amygdala activity in the BPD patients

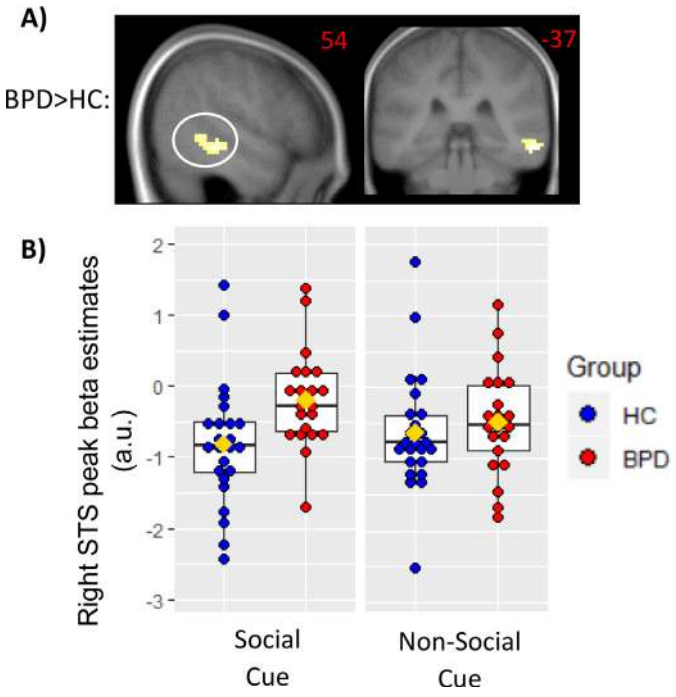

Fig.. 2. Model 1 whole brain fMRI results for the Social Condition by Group Cue Contrast. A) Whole brain analysis results from Model 1 showing the contrast social > non-social cues. The STS (yellow cluster) was shown to be significantly more activated by the BPD patients (95 consecutive voxels, peak [60 −37 −14]). Images are thresholded at $p = .001$, $k > 88$, Monte Carlo corrected and overlaid on the averaged normalized T1-weighted anatomical images created from all participants ($N = = 45$). B) Dot plots of the beta estimates extracted from an 8 mm sphere around the peak STS (from A). Average estimates of each category are illustrated by the yellow diamonds. a.u. = arbitrary units; BPD = borderline personality disorder patients; HC = healthy controls; STS = superior temporal sulcus.

for the social loss (versus non-social loss) contrast negatively correlated with CTQ physical abuse subscale ($\rho = -0.46$, $p = .036$; but not CTQ total score, $\rho = -0.35$, $p = .12$). However, this effect did not survive correction for multiple comparisons for all subscales employed (see Supplementary Table S6 for more detail).

3.1.2.3. Model 3: independent samples t-test regression analysis. Finally, to test the H3, that the processing of the cues by frontal regions would be related to dysfunctional negative social feedback processing, we entered the beta estimates from the bilateral amygdala ROI as a covariate in an independent samples *t*-test for social versus non-social cues, for each group separately (Fig. 4A). This analysis revealed a negative relationship for the BPD group in the left putamen/caudate, the bilateral middle frontal gyrus, and the pgACC (see Supplementary Table S3). There were no significantly activated voxels in the HCs (positive nor negative). A direct group comparison showed that the pgACC-amygdala coupling changed significantly between BPD patients and HCs. To better characterize this relationship, we extracted the beta estimates from the pgACC and conducted a correlation in each group with the beta estimates from the amygdala. We found a strong negative relationship in the BPD group (Fig. 4B; $\rho = -0.74$, $p < .001$) but not the HCs ($\rho = 0.31$, $p = .146$). More specifically, increased pgACC activity during the social versus non-social cue was followed by decreased activity in the amygdala during the processing of the negative social feedback in the BPD group but not the HCs. Please also note, conducting the same analysis, but utilizing the amygdala activity extracted from the positive social feedback (i.e. social win > non-social win) as a covariate in an independent samples *t*-test for social > non-social cues did not reveal any significantly activated voxels for either group alone,

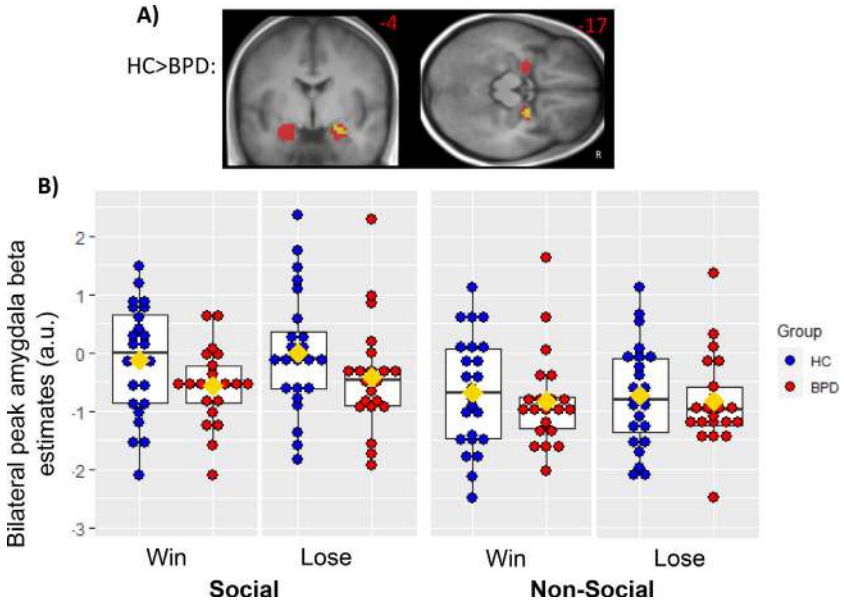

Fig.. 3. Model 2 amygdala ROI activation in the interaction Social Condition by Group Feedback Contrast. A) Significant amygdala ROI activation is shown in yellow (right: 26 consecutive voxels, peak [21 −1 −14], t = =3.57, p_{FWE} =0.007; left: 1 voxel, peak [−18, −4, −14], t = =2.90, p_{FWE} =0.048) in the 2-way interaction (Social Condition x Group) overlaid on the ROI mask created using the WFU PickAtlas (red). ROI activations are shown with p=.05 FWE corrected, and overlaid on the averaged normalized T1-weighted anatomical images created from all participants. B) Dot plots underlaid by boxplots of the beta estimates extracted from the bilateral amygdala mask (i.e. red voxels in A). Average estimates of each category are illustrated by the yellow diamonds. a.u. = arbitrary units; BPD = borderline personality disorder patients; HC = healthy controls; ROI = region of interest.

nor in the contrast between the two. Hence, our evidence of altered pgACC-amygdala coupling in BPD (relative to HCs) was restricted to the relationship between social anticipation and *negative* social evaluation.

4. Discussion

We utilized fMRI to investigate how BPD patients (compared to HCs) process socially relevant signals (cues and feedbacks) compared to non-social signals. The overarching goal of this study was to understand how anticipatory social cues and subsequent performance-based socially evaluative signals are coded and integrated in this clinical population. BPD patients showed a stronger signal than HCs in left STS while processing social anticipatory cues (compared to non-social cues). During the processing of performance-based socially evaluative feedback, BPD patients exhibited less activity than HCs in the right amygdala. Differential amygdala activity during the negative (but not the positive) social feedback evaluation was also modulated by prior pgACC reactivity to social anticipatory cues in the BPD group, but not the HCs. This study provides support for the hypothesis that BPD patients express altered neural processing even during the anticipation of social stimuli (e.g. heightened STS activity; (Scherpiet et al., 2014)), as well an atypical relationship between frontolimbic regions across the timespan of a social interaction.

The results from Model 1 revealed an increased activation of the right STS in the BPD patients compared to the HCs while processing social versus non-social cues (i.e. social anticipatory cues). Although this region was not a part of our original hypothesis (i.e. the STS is not part of the frontolimbic network), this region is frequently implicated in mentalizing, face perception, social cognition, and is involved in decoding the intentions and dispositions of others (Allison et al., 2000; Narumoto et al., 2001; Frith and Frith, 2006). Additionally, the right STS has been shown to be sensitive to the perceived congruency between a person's action and their emotional expression (Vander Wyk et al., 2009), and has also been shown to be hyperactivated during an emotional empathy (and hypoactivated during cognitive empathy) task in BPD patients (Dziobek et al., 2011). Differential STS activity at this point (i.e. social anticipation) may also suggest a dysfunction by the BPD patients regarding the "social learning" (or even the facial processing) component required from the cues in this kind of task (e.g. (Fineberg et al., 2018)). However, given that we did not find any other evidence supporting a faulty processing of facial expressions in the patients (e.g. no differences between the reaction times, and no other differences in brain areas specialized for face processing), we can reasonably assume that this was not a confounding factor. Rather, this pattern of results suggests that the social cues were acutely relevant (i.e. highly salient) for the patients in our experiment, which is in-line with both BPD characteristics and clinical observations.

The results from Model 2 indicate that, when processing social versus non-social feedback, the BPD patients expressed less activity than HCs in the bilateral amygdala, a brain region which detects emotional salience from faces (Adolphs, 2010). Decreased response in this region points to a reduced reactivity to evaluative social feedback signals in BPD. From the findings in Model 1 and 2 together, we can speculate that BPD patients may rapidly detect social cues indicative of potentially adverse consequences (resulting in increased STS activity), while they would then suppress limbic responses to upcoming negative social feedback. It should be noted that although the amygdala was originally implicated in the processing of negative emotional stimuli (particularly fear), it is also an integral node in the "social brain", much like the STS, and together these regions play an important role in social cognition (Adolphs and Spezio, 2006; Kennedy and Adolphs, 2012). Thus, these results further highlight differential processing of social stimuli by BPD patients. Intriguingly, amygdala activity for the negative social (versus non-social) feedback negatively correlated with the degree of childhood physical abuse in the BPD patients, i.e., heightened childhood physical abuse likely exacerbated dampened limbic emotional reactivity. It is possible that those who suffered from physical abuse in childhood may have developed a coping strategy (Crowell et al., 2009), which is reminiscent of trauma-related dissociation characteristic of these patients (see (Krause-Utz and Elzinga, 2018)). However, given the fact that this correlation was not corrected for multiple comparisons, this result requires further investigation/verification before any conclusions can be solidified.

Finally, the results from Model 3 revealed that, solely in the BPD group, the reduced amygdala response to negative social feedback was inversely related to anticipatory activity in the pgACC, left putamen/caudate, and bilateral middle frontal gyrus. Furthermore, the degree of pgACC-amygdala coupling was also significantly different between the two groups. The higher the pgACC activation during the processing of the social anticipatory cue, the less the amygdala reactivity during the processing of the negative social feedback in the BPD patients compared to the HCs. These results are particularly interesting because the pgACC is not only involved in automatic forms of emotion regulation (Etkin et al., 2011), but has also been shown to suppress limbic

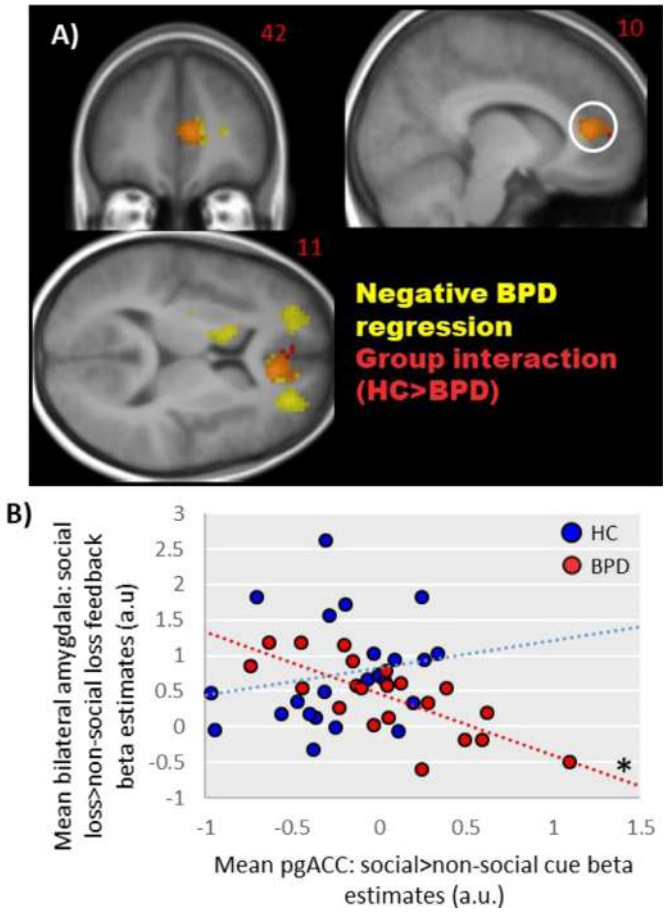

Fig.. 4. Model 3 Whole-brain fMRI results from the independent samples *t*-test amygdala feedback regression analysis. A) The change in signal (i.e. beta estimates) from the bilateral amygdala ROI (Fig. 2) was extracted from the processing of the social loss > non-social loss feedback and entered as a covariate in an independent samples *t*-test for each group (i.e. HCs and BPDs) testing the difference between the processing of the social > non-social cues. The negative regression in the BPD group is shown in yellow and includes the pgACC, bilateral middle frontal gyrus, and left putamen. The main effect of group (i.e. HC > BPD) is shown in red (and the overlap is shown in orange), and includes solely the pgACC (93 consecutive voxels, peak [9 41 10], $t = =4.97$). B) Illustration of the above-mentioned modulation. The y-axis shows the extracted amygdala activity (which was entered as a covariate in the fMRI model), and the mean pgACC activity extracted from A (white circle) is shown on the x-axis. There was a significant correlation in the BPD group (rho = −0.74, $p < .001$) but not the HCs (rho = 0.31, $p = .146$).*$p < .05$; a.u. = arbitrary units; BPD = borderline personality disorder patients; HC = healthy controls.

reactivity following negative emotion induction in non-clinical, healthy participants (Etkin et al., 2011; Schiller and Delgado, 2010), and may thus resolve heightened emotional conflict via top-down inhibition of the amygdala (Etkin et al., 2006). In line with these findings, Carlson and colleagues (Carlson et al., 2013) showed that healthy individuals with a bias for increased attention to threatening stimuli expressed an increase in functional coupling between the amygdala and pgACC. Further, in a recent meta-analysis, Marusak et al. 2016 proposed that dysfunctional resting-state connectivity between the pgACC and amygdala may reflect a common neurobiological substrate (referred to in the paper as a "functional fingerprint") in disorders that express heightened internalization and dysfunctional emotional processing (thus including BPD; (James and Taylor, 2008)). However, this meta-analysis included only one study (out of 46) with a sample of BPD patients. Therefore, we would like to speculate that this pattern of results (i.e. the relationship between pgACC social cue anticipation and amygdala negative social feedback processing) provides support for the idea that impaired pgACC-amygdala connections may contribute to dysfunctional social processing in BPD.

Taken together, the present findings demonstrate that BPD patients express an exacerbated neural reactivity to social anticipatory cues (i.e. heightened STS), as well as an atypical relationship between the pgACC and amygdala, whereby pgACC relates to a top-down suppression/inhibition of limbic activity during the processing of negative social feedback. Further supporting this interpretation, the pgACC-cue and amygdala-feedback relationship was only observed for the negative social feedback, and not for the positive social feedback. This pattern of activation could reflect a form of coping that the patients have been conditioned to engage in, possibly via increased childhood abuse, in order to alleviate the impact of the negative feelings arising from negative evaluative social feedback (or from negative social signals in general). Thus, when the patients actually receive negative feedback, or feedback that is only slightly negative (e.g. an angry face is obviously less negative than physical abuse), they are unable to process this information in an emotionally adaptive way (e.g. decreased amygdala activity) and may thus also react inappropriately to it. This is in line with several developmental models of BPD, such as Linehan's model (e.g. (Crowell et al., 2009; Linehan, 1993)) whereby heightened emotion dysregulation results in distorted information processing and can then lead to shutting down/freezing resulting in dissociation.

The present findings expand on previous work in several ways. In particular, our results suggest a possible progression of dysfunction throughout social interactions (i.e. from social anticipatory processing, through to the processing of the feedback) in these patients. It is reasonable to speculate that these patients do not exhibit atypical responses solely during the processing of feedback (i.e. during the social interaction itself), but also during the mere anticipation of the upcoming socially evaluative context. These conclusions are promising, particularly for creating new targeted treatment options for these patients. For example mindfulness training (e.g. (Atkinson, 2013)) or neurofeedback (e.g. (Mennella et al., 2017)) may be utilized in order to decrease the anxiety and negative feelings associated with an upcoming social interaction (i.e. social anticipation). This could then have a cascading positive effect on social functioning within this patient population. Additionally, given the heightened STS activity at the onset of the social cue, utilizing more mentalization based treatments could likely have long-lasting significant effects on BPD symptomatology (Bateman and Fonagy, 2010). Finally, the overarching ideas investigated in this paper (namely understanding how the amygdala is modulated by previously seen stimuli) have impactful consequences for clinical research. The vast majority of fMRI studies have shown atypical recruitment of the amygdala in this patient population (for a meta-analysis see (Schulze et al., 2016)), yet few have aimed to investigate how this differential processing might unfold across the time-span of a social interaction beyond simply resting-state connectivity. Aside from the development of new intervention strategies, understanding how the amygdala is affected by up- and down-stream connections throughout a social interaction may ultimately help to elucidate the neural bases of interpersonal dysfunction in BPD.

The main limitation of the present study relates to the fact that many of the BPD patients were medicated during scanning. Including only medication-free patients could have created a selection bias in our sample, while removing current medications was not possible due to ethical implications and could have had other negative effects linked to the momentary increase in symptomatology. Thus, patient medication may have an effect on differential activity seen in the relative brain signal, especially for the amygdala (see (Schulze et al., 2016)). Additionally, several of our patients were diagnosed with comorbid disorders (particularly depression and ADHD). Even though we carefully checked for any interactions between medication load or comorbid disorders and brain activations (see Supplementary Tables S4-5), we cannot fully rule them out as confounding factors. It should however be noted that the majority of the general BPD population is medicated (up

to 84%) (Hörz et al., 2010), and also present with comorbid disorders (Zimmerman and Mattia, 1999; Skodol et al., 2005), therefore likely increasing the generalizability of our results. In addition, we cannot conclude that the results in this manuscript are specific to BPD patients, as we did not include another non-BPD patient cohort. Finally, we also chose to utilize a paradigm where the cue itself was social (i.e. a neutral face) rather than the traditional symbol that is often used with social incentive delay tasks (e.g. (Spreckelmeyer et al., 2009)). Thus, we cannot conclude for certain that the effect of the social cue was specifically related to the "emotional" response elicited by the face, the anticipation of the upcoming feedback, or both. In a real-world setting however, we can suggest that there is likely a mix between both aspects, thus again potentially increasing the generalizability of these results.

In conclusion, our findings suggest an alteration of the neural processing of social signals in BPD. This supports the notion that BPD is a disorder characterized not only by atypical amygdala activity during emotion processing, but by a differential frontolimbic relationship, which may result in difficulties adapting in the context of a social situation. It is possible that these results may help to explain why BPD patients are unable to produce adapted responses regarding relevant environmental information, particularly salient social information (Crowell et al., 2009; Vega et al., 2013). These results help to explain why BPD patients suffer from pervasive difficulties in adjusting their behavior, particularly in the context of interpersonal relationships.

5. Financial disclosures

None

CRediT authorship contribution statement

Kimberly C. Doell: Conceptualization, Methodology, Software, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing, Visualization, Project administration. **Emilie Olié:** Conceptualization, Methodology, Investigation, Writing - review & editing, Visualization, Project administration, Funding acquisition. **Philippe Courtet:** Conceptualization, Supervision. **Corrado Corradi-Dell'Acqua:** Methodology, Software, Formal analysis, Writing - review & editing. **Nader Perroud:** Conceptualization, Resources, Supervision. **Sophie Schwartz:** Conceptualization, Methodology, Formal analysis, Resources, Writing - review & editing, Visualization, Supervision, Funding acquisition.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nicl.2019.102126.

Appendix I

The relevant anonymized data for this article can be found at: https://osf.io/nbw6h/?view_only=cb6c6fb8744643ee9477f77910891495

And the relevant unthresholded functional maps can be found at: https://identifiers.org/neurovault.collection:6034.

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