Brain Topography (2019) 32:753–761
https://doi.org/10.1007/s10548-019-00712-0

ORIGINAL PAPER

Neural Signatures of Social Inclusion in Borderline Personality Disorder Versus Non-suicidal Self-injury

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Received: 23 December 2018 / Accepted: 16 April 2019 / Published online: 22 April 2019

Abstract

Borderline personality disorder (BPD) is characterized by interpersonal disturbances and dysfunctional behavior such as non-suicidal self-injury (NSSI). We recently observed neural alterations in BPD during social inclusion by enhanced activations within the dorsomedial prefrontal cortex (dmPFC) and the posterior cingulate cortex (PCC). To examine the specificity of these neural alterations, we now investigated participants with NSSI but without BPD and compared them to BPD and healthy controls (HC). Considering the association between NSSI and BPD, we further examined neural commonalities during social inclusion. Fifteen females diagnosed with BPD, 16 with NSSI and 17 HC were investigated by fMRI and the cyberball paradigm, focusing on social inclusion ($p<0.05$; FWE on cluster-level). To examine neural commonalities between BPD and NSSI compared to HC, we computed a conjunction analysis on neural activations under social inclusion. Significant increases in neural activation were observed in BPD within the dmPFC under social inclusion compared to NSSI and HC, whereas neural activations within the PCC did not differ between BPD and NSSI. The conjunction analysis revealed a common neurofunctional increase within the pregenual anterior cingulate cortex and the anterior insula in both, BPD and NSSI. We provide a further evidence regarding a disorder-specific neural reactivity within the dmPFC during social inclusion in BPD, whereas PCC activations may represent an unspecific neural alteration in BPD when compared to NSSI. In contrast, both clinical groups revealed a common neural increase within the salience network that may support the assumptions of a developmental continuum between these two psychiatric conditions.

Keywords Borderline personality disorder · Non-suicidal self-injurious behavior · fMRI · Cyberball · Social interaction

Introduction

Borderline personality disorder (BPD) is clinically characterized by emotional instability, interpersonal disturbances and impulsive, dysfunctional behavior such as non-suicidal self-injury (NSSI) (American Psychiatric Association 2013). Investigating the impairments in interpersonal functioning in BPD revealed the tendency to misinterpret neutral situations in terms of feeling rejected during normative inclusion conditions (Lis and Bohus 2013). More recently, neuroimaging studies expanded these findings by demonstrating potential underlying neurofunctional alterations of these misinterpretations (Lis and Bohus 2013). Domsalla et al. (2014) investigated patients with BPD compared to healthy controls (HC) by functional magnetic resonance imaging (fMRI) and the established cyberball paradigm and examined neural correlates of social exclusion and inclusion. Of note, they demonstrated relatively increased neural activations within

Handling Editor: Stefano Seri

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10548-019-00712-0) contains supplementary material, which is available to authorized users.

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the dorsomedial prefrontal cortex (dmPFC) and the precuneus under social inclusion in BPD and thus, neural alterations within brain regions previously assigned to emotional conflict monitoring and self-referential mentalizing in HC (Atique et al. 2011; Etkin et al. 2011). Although pronounced under social inclusion, subjects with BPD showed almost similar neural reactivity during social exclusion and inclusion. These results suggested an impaired discrimination between social situations accompanied by enhanced neural emotional conflict monitoring and hypermentalizing processes, even under social inclusion conditions (Domsalla et al. 2014). We have recently expanded this observation of neural alterations under social inclusion in a sample of BPD and controlled for comorbid major depression (MD) and antidepressant medication by the inclusion of a clinical control group (Malejko et al. 2018). Results were again in favor of a disorder-specific neural alteration in BPD under social inclusion by enhanced neural activations within the dmPFC and the posterior cingulate cortex (PCC).

To further examine the specificity of neural alterations in BPD under social inclusion, we now included an additional clinical control group with typical BPD-like symptoms, i.e. young female adults with non-suicidal self-injurious behavior (NSSI) but without BPD. NSSI is defined as the deliberate, self-inflicted destruction of body tissue without suicidal intent and has been suggested as an independent diagnostic entity in the DSM-5 (American Psychiatric Association 2013). By fMRI and the cyberball paradigm, we previously studied adolescents with NSSI but without BPD and a sample of significantly older adult BPD patients that overlaps with the sample presented here (Brown et al. 2017). We confirmed previous findings of enhanced neural dmPFC activations but also found increased neural activations within the anterior insula upon social inclusion in BPD. Interestingly, both clinical groups, adolescents with NSSI and adult BPD, showed increased neural activation versus HC within the ventral anterior cingulate cortex (vACC) under social exclusion. Considering the general consensus regarding an association between NSSI and BPD (Zetterqvist 2015) and the observation that early age of NSSI-onset is associated with an increased risk of developing BPD later on in life (Groschwitz et al. 2015), we suggested that NSSI and BPD might represent a developmental continuum, starting with an increased sensitivity to social exclusion in adolescence within the salience network (vACC and anterior insula) that may generalize to neutral or even positive social situations in later NSSI or BPD. However, direct comparisons between these two clinical groups were not eligible due to significant effects of age (Brown et al. 2017). This motivated the investigation of an adult sample with NSSI but without BPD in our current study design.

Taking suggestions of NSSI as a distinct psychiatric condition and not only a symptom of BPD into account (American Psychiatric Association 2013), we hypothesized that an impaired discrimination between social situations and thus, enhanced neural emotional conflict monitoring and hypermentalizing processes even under social inclusion conditions (Domsalla et al. 2014), is specific to BPD and not evident in NSSI without BPD. According to our previous study (Malejko et al. 2018), we particularly assumed relatively enhanced neural alterations within the dmPFC and the PCC under social inclusion as potential disorder specific neural signature in BPD as compared to NSSI. Apart from examining this specificity of neural alterations in BPD during social inclusion, our present study was also designed to examine potential commonalities in neural activations between now age-matched groups of participants with BPD with NSSI and NSSI without BPD. Furthermore, we expected a common neural response within major regions of the salience network such as the vACC and the anterior insula in BPD and NSSI as both regions are highly correlated to the affective appraisal of social interaction situations and alterations within these regions have been previously described in BPD with NSSI (Domsalla et al. 2014), but also in NSSI without BPD (Bonenberger et al. 2015).

Materials and Methods

Subjects

We investigated data from 15 adult patients with BPD and non-suicidal self-injurious behavior (23.3 years; SD 4.13) and 17 HC (23.1 years; SD 4.26). Only female participants were included in this study and except of two left-handed subjects in the NSSI-group, all other participants were right-handed as assessed by the Edinburgh Handedness Scale. Clinical data of the investigated BPD-patients were already reported in Malejko et al. (2018) (see also Tables S1 and S2). Data from the sample of 16 adult females with NSSI but without a diagnosis of BPD (20.9 years; SD 2.64) were reported in the context of another fMRI task in Bonenberger et al. (2015). Of note, both patient groups and HC did not significantly differ in age ($F(2,42) = 1.74$, $p = 0.188$) or education ($F(2,42) = 0.31$, $p = 0.733$). Within the NSSI-group, one subject had a history of MD, one subject had agoraphobia and two subjects had an additional diagnosis of a specific phobia. Two subjects within the NSSI-group reported BPD as a presumptive diagnosis for clinical treatment during adolescence, and two reported of a history of eating disorder (bulimia nervosa). Of note, none of them had current clinical symptoms. One patient within the NSSI-group took one antidepressant that was however, not recorded. None of the HC took any kind of medication or had a current or lifetime psychiatric diagnoses or NSSI. Regarding the quantity of non-suicidal self-injurious behavior, patients within the

BPD- and the NSSI-group reported similar mean lifetime NSSI-events ($p = 0.713$). However, within the last month, non-suicidal self-injurious behavior was more frequent in the BPD-group (4.4 events, SD 4.72) compared to subjects with NSSI (0.14 events, SD 0.53; $p = 0.000$). All subjects in the BPD- and the NSSI-group mainly engaged in skin-cutting as the predominant form of NSSI. Further details are provided in our Table S1.

Participants were recruited from the Department of Psychiatry and Psychotherapy of the University Hospital Ulm. Participants with any severe medical disorder, epilepsy, substance use disorder and psychotic disorders were excluded from the study. All participants gave written informed consent prior to the study that was approved by the local ethical committee and conducted in accordance with the Declaration of Helsinki.

Psychometric Measures

Clinical diagnoses of BPD and a history of NSSI were verified by one of the study physicians using the Structured Clinical Interview for DSM-IV (First et al. 1997). To assess details on present and lifetime NSSI, we used the semi-structured Self-injurious Thoughts and Behaviors Interview (SITBI; Fischer et al. 2014). Borderline symptom severity was assessed by the Borderline Symptom List (BSL-23; Bohus et al. 2007), current depressive symptoms were examined by the Beck Depression Inventory (BDI-II; Hautzinger et al. 2006). The Hurt-Feelings-Scale (HFS; Leary and Springer 2001) was used to examine general sensitivity for social exclusion. This scale consists of eight questions concerning emotional reactivity in social situations. Each question is rated on a 5-point Likert-scale and higher total scores correspond to higher sensitivity to social exclusion.

To assess emotional reactions elicited by the fMRI-paradigm, we used the 20-item Need-Threat-Scale (NTS; Jamieson et al. 2010) with its four subscales (feeling excluded, low self-worth, meaningless existence, control) with five items each. Each item was rated on a scale from 1 (not at all) to 5 (very much) and total scores were calculated by dividing the final result by 20, resulting in a range from 1 (very high distress) to 5 (no distress). A one-way analysis of variance (ANOVA) and post hoc Newman–Keuls tests were computed to analyze psychometric scales. The statistical threshold of significance was set to $p < 0.05$. To consider multiple comparisons of the ANOVAs in dependent measures (NTS and feelings after fMRI), we applied a false-discovery rate (FDR) correction at $p < 0.05$.

fMRI Paradigm

To investigate social inclusion during fMRI and to warrant comparability with previous investigations, we used the cyberball paradigm in its original design (Williams et al. 2000). Subjects were instructed to take part in the virtual ball-tossing game with two other participants supposed to be in another room. In fact, participants played against the computer and all actions were pre-programmed (Williams et al. 2000). The tasks consisted of three different conditions (passive watching, social inclusion and social exclusion). Each condition was applied once, lasting around 2 min (60 throws). During the passive watching condition, subjects were asked to just watch the game and the computer controlled their character. In the inclusion condition, participants had a random ball possession in one third of tosses and chose which of the other players to throw the ball by a right index or middle finger key press response. The exclusion session started with 10 throws of 30% randomized ball possession and then subjects were excluded from the game for the remaining 50 throws. After fMRI-scanning, subjective emotional experiences were assessed regarding predefined indicated feelings (see Table 1) on a visual rating scale ranging from 1 (very low) to 4 (very strong). Information about the necessity of deception in this experiment and the real nature of the cyberball game was given in a debriefing session after this assessment. Of note, we found no hints that participants did not believe the cover story, all subjects expressed surprise when they were told the cover story and none of the subjects had to be excluded for this reason.

fMRI Data Acquisition

Functional imaging data were acquired by a 3-T MAGNETOM Allegra (Siemens) scanner. A T2*-sensitive gradient echo sequence was used for functional imaging with an echotime (TE) of 33 ms, a flip angle of 90°, a field of view of 230 mm, and a slice thickness of 2.5 mm with an interslice gap of 0.5 mm. Repetition time (TR) was 2000 ms and 35 transversal slices were recorded with an image size of 64×64 pixels during the cyberball task. Anatomical high-resolution T1-weighted images ($1 \times 1 \times 1$ mm voxels) were acquired (band-width (BW) 130 Hz/Pixel, TR 2500 ms, TI 1.1 s, TE 4.57 ms, flip angle 12°) for reasons of coregistration and normalization into standardized stereotactic space.

fMRI Data Analysis

Image pre-processing and statistical analyses were carried out using Statistical Parametric Mapping (SPM12) with a random effects model for group analyses. Data from each session were pre-processed including slice-timing, realignment and normalization into a standard template (Montreal Neurological Institute, MNI) with a spatial resolution of $2 \times 2 \times 2$ mm^3. Smoothing was applied with an 8-mm FWHM isotropic Gaussian kernel. Intrinsic autocorrelations were accounted for by AR (1) and low frequency drifts

Table 1 Results of psychometric measurements in HC, patients with BPD and participants with non-suicidal self-injury without BPD (NSSI)

	HC		BPD		NSSI		One-way ANOVA		Post hoc Newman–Keuls (p)		
	Mean	SD	Mean	SD	Mean	SD	F (2,42)	p	HC versus BPD	HC versus NSSI	BPD versus NSSI
BDI	3.2	3.95	40.1	13.72	12.2	8.49	64.11	0.000	0.000	0.013	0.000
BSL	0.21	0.25	2.45	1.28	0.58	0.73	30.34	0.000	0.000	0.241	0.000
HFS	18.2	4.51	27.1	3.50	18.2	2.17	30.16	0.000	0.000	0.985	0.000
NTS total-score	2.8	0.70	1.59	0.40	2.5	0.66	18.02	0.000*	0.000	0.137	0.000
Feelings after fMRI											
Angry	1.2	0.64	2.3	0.14	1.2	0.58	8.73	0.001*	0.002	0.900	0.001
Sad	1.4	0.70	2.1	1.03	1.1	0.36	7.11	0.002*	0.006	0.446	0.002
Happy	2.6	0.80	1.4	0.84	2.4	0.94	8.98	0.001*	0.001	0.614	0.002
Afraid	1.2	0.44	2.3	1.07	2.1	1.07	6.22	0.004*	0.007	0.014	0.512
Frustrated	1.4	0.70	2.2	1.05	1.1	0.53	7.41	0.002*	0.005	0.470	0.002
Satisfied	2.6	0.62	1.4	0.94	2.6	1.15	8.19	0.001*	0.001	0.871	0.002
Helpless	1.5	1.07	2.5	1.16	2.2	1.31	2.83	0.071			
Inner tension	1.8	0.73	2.8	0.80	2.3	0.99	5.03	0.011*	0.009	0.141	0.112

To control for multiple comparison of the ANOVAs in dependent measures (NTS and feelings after fMRI), a FDR correction was applied significant at $p < 0.05$ (FDR-corrected) to interfere significant main effects (*)

BDI beck depression inventory, *BSL* borderline symptom list, *HFS* Hurt Feeling Scale, *NTS* Need Threat Scale; numeric scales of 'feelings after fMRI' range from 1 (very low) to 4 (very strong); *SD* standard deviation, *vs* versus, *ANOVA* analysis of variance

were removed via high-pass filtering. For individual first level analyses, a general linear model was set up with the cyberball task modeled as three separate blocks of condition (passive watching, inclusion, exclusion) according to Eisenberger et al. (2007). Regressors representing the six motion parameters were integrated into the design matrix. After model estimation, beta-images representing the averaged, estimated magnitude of neural activation associated with passive watching, inclusion and exclusion were computed for each participant.

According to our hypothesis, individual differential contrast images comparing social inclusion minus passive watching served for second level group analyses. Within a full-factorial model, we focused on neural differences between BPD and NSSI and computed one tailed t-contrasts for between-group-differences at a statistical level of significance of $p < 0.001$ at the voxel-level and at least 160 contiguously significant voxels corresponding to family-wised error (FWE) correction of $p < 0.05$ on cluster level. In addition, to examine conjointly significant clusters of differential neural activations in BPD and NSSI compared to HC, we computed a conjunction analyses as provided by SPM at a less conservative statistical threshold of $p < 0.001$ at the voxel level. In case of significant voxel activation within the salience network (e.g. vACC and/or the anterior insula) as outlined above, we applied a FWE-correction ($p < 0.05$) for search volume within a sphere of 5 mm. This analysis was computed for exploratory purposes considering that statistical inference on equality of neural activations within the two clinical groups compared to HC would require much higher sample sizes as in this study. To examine whether differential neural activations (social inclusion minus passive watching) were associated to psychometric measures, we computed correlation analyses on differential parameter estimates and sum-scores within each group.

Results

Psychometric Measurements

In line with the clinical diagnosis and the high comorbidity of MD in BPD (Distel et al. 2016), significant higher BSL- and BDI-scores were observed in BPD compared to HC and NSSI, whereas the NSSI-group and HC did not differ. General sensitivity for social exclusion as examined by the HFS was significantly higher in BPD compared to HC and NSSI, whereas HC and the NSSI-group also did not differ. Ratings regarding the subjective experience of the fMRI-paradigm revealed significant higher NTS-scores in BPD compared to both, NSSI and HC. Also here, NSSI and HC did not differ. Patients with BPD significantly felt more angry, sad, afraid, frustrated, inner tense and less happy or satisfied compared to HC. Even when compared to NSSI, patients with BPD felt more angry, sad and frustrated and less happy and satisfied. HC and NSSI differed only regarding the feelings of being afraid as the only communality with BPD in psychometric measurements (see Table 1).

fMRI Results

Comparisons of differential (social inclusion versus passive watching) neural activations between BPD and HC have been recently reported in Malejko et al. (2018). Shortly, a relatively enhanced neural reactivity was observed within the right dmPFC and the right PCC in BPD versus HC but also compared to patients with MD.

Now comparing young adults with BPD with young adults with NSSI, we again revealed a significant increase in differential neural activations within the right dmPFC in BPD relative to NSSI (Fig. 1a). Against our previous assumption, we found no significant enhanced neural activations within the PCC in BPD under social inclusion compared to NSSI. No significantly enhanced differential neural activations were observed in the reverse contrast (NSSI > BPD) under social inclusion.

For exploratory purposes, we examined conjointly significant clusters of differential neural activations in BPD and NSSI each compared to HC, and observed a similar increase in differential neural activations in both clinical groups within the right pregenual anterior cortex (pgACC) and the left anterior insula ($p < 0.05$, FWE-corrected for search volume, see Fig. 1b). Further details on fMRI results are provided in our Table 2.

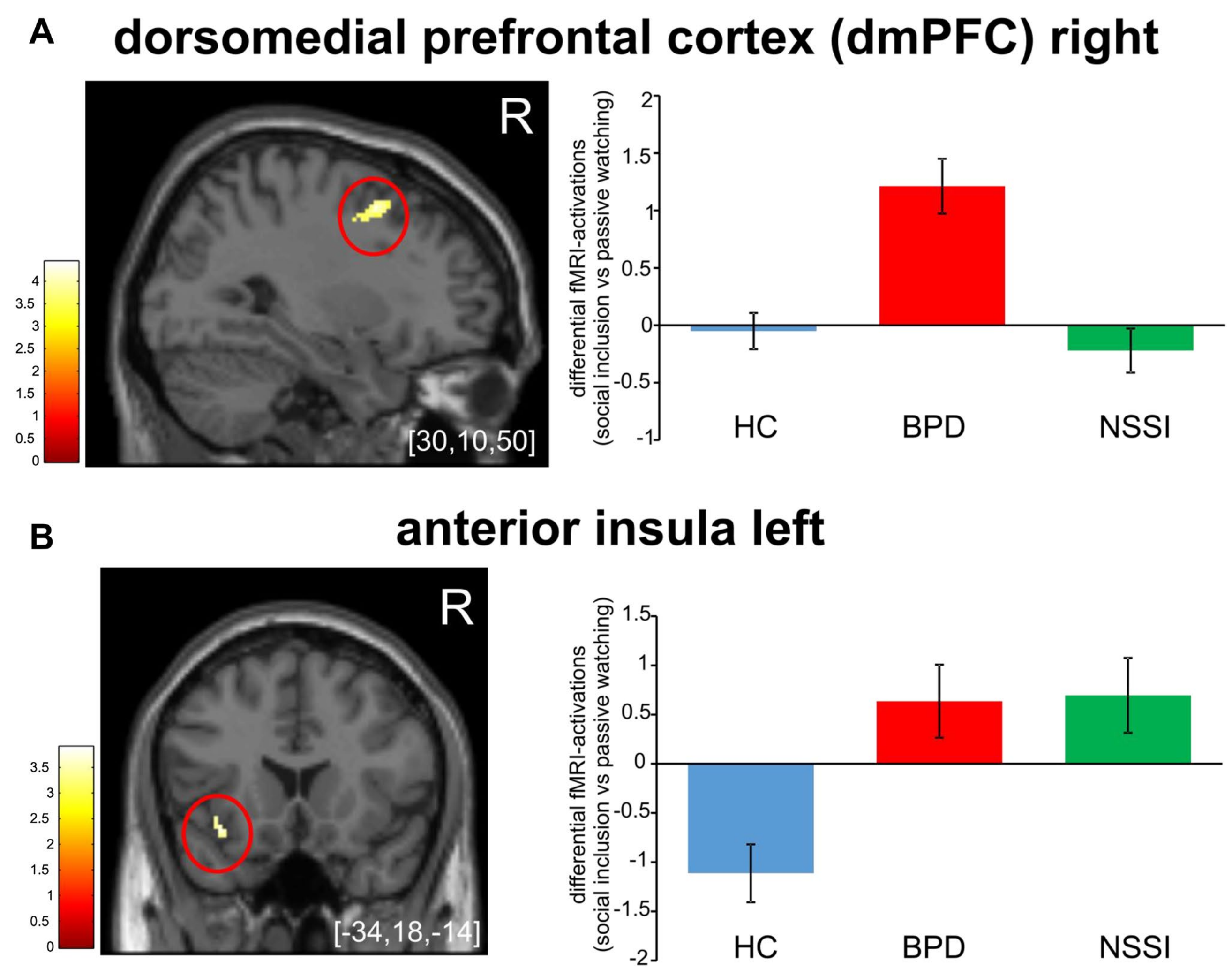

Fig. 1 fMRI results. **a** Significant ($p < 0.05$, FWE-corrected on cluster level) differential (social inclusion minus passive watching) neural activations within the right dmPFC in BPD compared to NSSI and compared to HC. For demonstrational purposes, we depict neural activations within the dmPFC at the threshold of $p < 0.001$ at the voxel-level and at least 160 contiguously significant voxels corresponding to FWE correction of $p < 0.05$ on cluster level. **b** Differential (social inclusion minus passive watching) neural activation within the left anterior insula as revealed by a conjunction analyses comparing BPD > HC + NSSI > HC at $p < 0.05$, FWE-corrected for a search volume (5 mm sphere from peak voxel activation). For demonstrational purposes, neural activations within the left anterior insula were depicted at the threshold of $p < 0.001$ uncorrected at the voxel-level. *HC* healthy controls, *BPD* borderline personality disorder, *NSSI* patients with non-suicidal self-injurious behavior without BPD, *R* right. MNI-coordinates are provided in mm in squared brackets

Table 2 fMRI results

Anatomic label	L/R	Cluster size NV	*Z*	*p*	MNI		
					x	*y*	*z*
BPD > NSSI							
dmPFC	R	179	3.99	0.032	34	0	46
	R		3.89		26	14	48
	R		3.77		36	4	58
BPD > HC + NSSI > HC (conjunction)							
Pregenual anterior cingulate cortex (pgACC)	R	20	3.58	0.004	12	50	− 2
Anterior insula	L	13	3.41	0.006	− 34	18	− 14

Significant ($p < 0.05$; FWE-corrected on cluster-level) fMRI results comparing differential (inclusion minus passive watching) neural activations between patients with borderline personality disorder (BPD) and with non-suicidal self-injurious behavior without BPD (NSSI) compared to HC during the cyberball task. We observed no significant enhanced neural activations under social inclusion in NSSI compared to BPD

A conjunction analysis to examine conjointly activated differential neural activations in NSSI and BPD compared to HC revealed significant differential neural activations within the pregenual anterior cingulate cortex and the anterior insula ($p < 0.05$; FWE-corrected for search volume within a 5 mm sphere over peak voxel activation)

BA Brodman area, *L* left, *R* right, *NV* number of voxels, *Z* Z-value, *p p* value (FWE on cluster-level), *MNI* Montreal Neurological Institute (x-, y-, z-coordinates are provided in mm)

Correlation Analyses

To examine whether the significant increase in neural activation within the dmPFC that differed between BPD and NSSI, was associated with psychometric measures, we extracted differential fMRI parameter estimates for correlation analyses. As previously reported (Malejko et al. 2018), differential neural activations within the dmPFC cluster were significantly ($r = 0.55$; $p = 0.016$) correlated with BSL-sum-scores in BPD. Of note, we found no significant correlations within this cluster with the quantity (lifetime or within the last months) of NSSI. Considering the significant differences compared to HC in differential neural activations within the pgACC and the anterior insula in both, BPD and NSSI, we computed correlational analyses to examine the relation of these increases with the quantity of NSSI. Again, this correlation analyses revealed no significant results.

Discussion

We recently demonstrated neural alterations in BPD during social inclusion compared to MD and HC (Malejko et al. 2018) as a potential disorder-specific neural signature of misinterpretations of social interactions. To further examine the specificity of these neural alterations, we now investigated a sample of adult female patients with BPD-like symptoms such as NSSI but without BPD, and compared neural activations during social inclusion with those observed in our previously investigated samples of female patients with BPD and HC. According to the clinical diagnoses and in line with previous investigations (Bungert et al. 2015), borderline symptoms and general sensitivity for social rejection were significantly more evident in young adults with BPD compared to both, NSSI and HC, whereas scores in the NSSI group did not differ from HC. In line with the known high comorbidity of BDP and MD (Distel et al. 2016), clinically relevant depressive symptoms were observed in BPD, but differed also between NSSI and HC. After the cyberball paradigm, patients with BPD reported higher subjective distress (as measured by the NTS scale), more negative and less positive emotions compared to NSSI and HC, which has also been observed in other investigations (Renneberg et al. 2012; Staebler et al. 2011) even during social inclusion (Domsalla et al. 2014; Ruocco et al. 2010). During fMRI, we demonstrated a significant increase in differential (social inclusion minus passive watching) neural activation within the right dmPFC in BPD compared to both NSSI and as previously reported (Malejko et al. 2018), compared to HC. Against our hypothesis, we found no differences in social inclusion-related PCC activation when comparing BPD with NSSI. Moreover, we found no significant differential neural activations under social inclusion in NSSI compared to HC. To examine whether patients with BPD and participants with NSSI exert common neural activations in brain regions related to saliency under social inclusion compared to HC as outlined above, we computed a conjunction analysis that demonstrated conjointly significant differential neural activations within the left anterior insula and the right pgACC in both clinical groups compared to HC.

According to our hypothesis, we focused on differential neural activations under social inclusion to examine the specificity of neural alterations in BPD in this condition and in particular within the dmPFC and the PCC (Malejko et al. 2018). By increases in neural activation within the dmPFC under social inclusion in young adults with BPD with NSSI but not in young adults with NSSI without BPD, we provide further evidence for the hypothesis of a disorder-specific neural alteration in this region under social inclusion in BPD. Of note, this neural alteration was even evident when comparing BPD to patients with MD (Malejko et al. 2018). This result is not only supported by a previous investigation (Domsalla et al. 2014), but also by the observation that increased activations in the dmPFC under social inclusion were associated with individual borderline symptom severity, but not to the quantity of NSSI, indicating that patients with higher BPD symptom load reveal higher neural dmPFC activations under social inclusion. Considering the functional subdivisions of the mPFC (Amodio and Frith 2006), the dorsal parts such as the dmPFC are related to emotional conflict monitoring in social cognition tasks (Etkin et al. 2011; Ochsner et al. 2004). The dmPFC has also been critically involved in self-referential mentalizing about social knowledge (Mitchell 2008; Powers et al. 2013). Whereas activations within this region were commonly observed under social exclusion in HC (Eisenberger et al. 2003), an increase in neural activation in BPD during social inclusion may reflect conflicts to internal assumptions in this disorder on a neural level, considering the typical internal belief of BPD that others will reject them (Baer et al. 2012). In addition, absent neural alterations in the dmPFC under social inclusion in NSSI without BPD as opposed to BPD with NSSI behavior, may further support the conceptualization and diagnostic organization of NSSI as a distinct psychiatric disorder beyond to a mere symptom of BPD (American Psychiatric Association 2013).

Whereas enhanced neural activations within the PCC under social inclusion were previously suggested as disorder-related neural alteration in BPD (Malejko et al. 2018), significant increases within the PCC were not evident in BPD compared to NSSI in this study. Neural activations within the PCC were associated to self-referential processing (Brewer et al. 2013) and to a mentalizing network implicated in social situations (Corradi-Dell'Acqua et al. 2014). The present study does not support the specificity of neural alterations in the PCC during social inclusion in BPD and neural activations differed not between BPD with NSSI and NSSI without BPD. One may assume that self-referential or mentalizing processes triggered by social inclusion are evident in a similar extent in NSSI under social inclusion, but however, this remains speculative and awaits empirical replication since behavioral data on self-referential mentalizing were not specifically assessed.

Considering the general association between NSSI and BPD (Zetterqvist 2015) and the common neural activation within the vACC under social exclusion in adolescent NSSI and adult BPD (Brown et al. 2017), we previously suggested that an increased sensitivity to social exclusion in adolescents with NSSI may generalize to neutral or even positive social situations in later NSSI and/or BPD. To examine such potential common neural alterations under social inclusion in adult BPD and adult NSSI, we computed a conjunction analysis for exploratory purposes. Interestingly, we found a relative increase in neural activation under social inclusion within the pgACC and the anterior insula in both, BPD and NSSI compared to HC. Neural activations within these core regions of the salience network (Menon and Uddin 2010) were linked to the affective appraisal of the experience of social exclusion in HC (Eisenberger 2012; Somerville et al. 2006). A recent study expanded this conceptualization by showing that in particular the ACC and the anterior insula are involved in self-relevant social evaluation (Perini et al. 2018). Enhanced neural activations within these regions also under social inclusion were previously described in BPD (Domsalla et al. 2014) and related to a maladaption to characteristics of a social environment, irrespective of its emotional valence in BPD (Franzen et al. 2011) that may also be present in adults with NSSI without BPD. This is supported by the association between emotion dysregulation in NSSI over and above a BPD diagnosis, and a model that suggests a deficient ability to regulate emotions in an adaptive manner in NSSI (Andover and Morris 2014). Thus, similar neural alterations within these regions may potentially relate to common features of BPD and NSSI beyond the quantity of NSSI, considering the lack of significant correlations in our study. Whereas these results support our previous assumption regarding the generalization of neural alterations within the salience network even during positive social situations in later NSSI and/or BPD (Brown et al. 2017), we are aware that these conclusion have be considered carefully and follow-up studies during different developmental stages may provide the more appropriate design.

Moreover, the following shortcomings have to be considered. Emotional reactions corresponding to our task were assessed by the NTS and regarding predefined feelings after the whole fMRI-paradigm and not separately after each condition. This limited the interpretability of our emotional reactions, in particular to social inclusion, since they may be confounded by the order of task conditions (passive watching, social inclusion, social exclusion). Thus, subjective ratings after fMRI might have captured affective responses associated with social exclusion rather than inclusion. We therefore refrained from correlation analyses between these psychometric and fMRI-measures. Another confound may arise by the identical order of task conditions and we cannot entirely exclude sequence effects. However, previous studies conducted with the same paradigm suggested that mere order effects do not sufficiently explain neurofunctional responses to social exclusion (Kawamoto et al. 2012). In addition, a previous study (Domsalla et al. 2014) investigated patients with BPD and the cyberball paradigm within a pseudo-random sequence of the three conditions. They also focused on social inclusion and revealed similar neural alterations in BPD compared to HC as we found in our study. Another confound may arise due to the unbalanced motor responses when comparing social inclusion to passive watching conditions (Sebastian et al. 2011) and we cannot entirely exclude this restriction. However, we computed a conjunction analysis as an approximation to assess conjointly significant voxels of differential (social inclusion versus passive watching) neural activations in HC, BPD and NSSI, within an anatomical mask comprising the left (contralateral) precentral gyrus as provided by the Wake Forest University (WFU) pickatlas. Of note, we did not find any significant neural activations up to a lenient threshold of $p < 0.05$, uncorrected at the voxel level which suggests a considerable motor confound rather unlikely. Moreover, eight patients within our BPD group were also diagnosed with PTSD, in line with the high prevalence of comorbidity in BPD (Frías and Palma 2015). Thus, we cannot rule out potential effects of PTSD-symptoms on neural alteration under social inclusion although our results regarding the neural alteration within the dmPFC in BPD are in line with another study that investigated BPD without PTSD (Domsalla et al. 2014). We further cannot entirely rule out effects of antidepressant medication, but it is of note that our previous investigation compared this sample of BPD with MD-patients under comparable medication, revealed similar neural alterations within the dmPFC as observed in this study, comparing BPD with patients with NSSI without antidepressants. Moreover, we are aware that our conjunction analysis is not eligible for statistical inference assessing neural equality. However, proofs of equality would require sample sizes of patients with BPD and participants with NSSI without BPD that were beyond availability.

Conclusion

Based on our observations regarding a potential disorder-related neural signature in BPD under social inclusion (Malejko et al. 2018), we now investigated a sample of adults with NSSI but without BPD by fMRI and the cyberball paradigm. We aimed to further examine the specificity of neural alterations within the dmPFC and the PCC under social inclusion in BPD by including a second clinical control group with BPD-like symptoms. Comparing patients with BPD to participants NSSI, we revealed a significant increase in neural activation within the dmPFC in BPD, supporting the specificity regarding a disorder-related neural signature under social inclusion. In contrast, the absence of significant differences in differential neural activations within the PCC in BPD compared to NSSI restricts the interpretation of a specific disorder-related neural alteration within this region. According to the general association between NSSI and BPD and as demonstrated by our conjunction analyses, we observed a common neural alteration within core regions of the salience network under social inclusion in both, NSSI and BPD. This may support the previous assumption of a developmental continuum in these two psychiatric conditions, starting with an increased neural sensitivity to social exclusion in adolescents with NSSI that may generalize to neutral or even positive social situations in young adults with NSSI and/or BPD.

Compliance with Ethical Standards

Conflicts of interest Paul L. Plener was an investigator in clinical studies by Servier and Lundbeck phamaceuticals. He received a speaker's honorarium by Shire. He received research funding from the German Federeal Ministry of Education and Research, the German Federal Institute for Drugs and Medical Devices, the Baden-Wuerttemberg as well as the Volkswagen Foundation. Kathrin Malejko, Dominik Neff, Rebecca Brown, Martina Bonenberger, Birgit Abler and Heiko Graf declare that they have no conflicts of interest.

Ethical Approval All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent A written informed consent was obtained from all individual participants included in the study.

References

American Psychiatric Association (2013) Diagnostic and statistical manual of mental disorders, 5th ediion (DSM-5). Diagnostic Stat. Man. Ment. Disord. 4th edn. TR., 280. https://doi.org/10.1176/appi.books.9780890425596.744053

Amodio DM, Frith CD (2006) Meeting of minds: the medial frontal cortex and social cognition. Nat Rev Neurosci. https://doi.org/10.1038/nrn1884

Andover MS, Morris BW (2014) Expanding and clarifying the role of emotion regulation in nonsuicidal self-injury. Can J Psychiatry. https://doi.org/10.1177/070674371405901102

Atique B, Erb M, Gharabaghi A, Grodd W, Anders S (2011) Task-specific activity and connectivity within the mentalizing network during emotion and intention mentalizing. Neuroimage. https://doi.org/10.1016/j.neuroimage.2010.12.036

Baer RA, Peters JR, Eisenlohr-Moul TA, Geiger PJ, Sauer SE (2012) Emotion-related cognitive processes in borderline personality disorder: a review of the empirical literature. Clin Psychol Rev. https://doi.org/10.1016/j.cpr.2012.03.002

Bohus M, Limberger MF, Frank U, Chapman AL, Kuhler T, Stieglitz RD (2007) Psychometric properties of the Borderline Symptom List (BSL). Psychopathology 40:126–132. https://doi.org/10.1159/000098493

Bonenberger M, Plener PL, Groschwitz RC, Grön G, Abler B (2015) Differential neural processing of unpleasant haptic sensations in somatic and affective partitions of the insula in non-suicidal self-injury (NSSI). Psychiatry Res Neuroimaging 234:298–304. https://doi.org/10.1016/j.pscychresns.2015.10.013

Brewer JA, Garrison KA, Whitfield-Gabrieli S (2013) What about the "self" is processed in the posterior cingulate cortex? Front Hum Neurosci. https://doi.org/10.3389/fnhum.2013.00647

Brown RC, Plener PL, Groen G, Neff D, Bonenberger M, Abler B (2017) Differential neural processing of social exclusion and inclusion in adolescents with non-suicidal self-injury and young adults with borderline personality disorder. Front Psychiatry. https://doi.org/10.3389/fpsyt.2017.00267

Bungert M, Liebke L, Thome J, Haeussler K, Bohus M, Lis S (2015) Rejection sensitivity and symptom severity in patients with borderline personality disorder: effects of childhood maltreatment and self-esteem. Borderline Personal Disord Emot Dysregul. https://doi.org/10.1186/s40479-015-0025-x

Corradi-Dell'Acqua C, Hofstetter C, Vuilleumier P (2014) Cognitive and affective theory of mind share the same local patterns of activity in posterior temporal but not medial prefrontal cortex. Soc Cogn Affect Neurosci. https://doi.org/10.1093/scan/nst097

Distel MA, Smit JH, Spinhoven P, Penninx BWJH (2016) Borderline personality features in depressed or anxious patients. Psychiatry Res. https://doi.org/10.1016/j.psychres.2016.05.007

Domsalla M, Koppe G, Niedtfeld I, Vollstädt-Klein S, Schmahl C, Bohus M et al (2014) Cerebral processing of social rejection in patients with borderline personality disorder. Soc Cogn Affect Neurosci 9:1789–1797. https://doi.org/10.1093/scan/nst176

Eisenberger NI (2012) The pain of social disconnection: examining the shared neural underpinnings of physical and social pain. Nat Rev Neurosci. https://doi.org/10.1038/nrn3231

Eisenberger NI, Lieberman MD, Williams KD (2003) Does rejection hurt? An FMRI study of social exclusion. Science (80-.) 302:290–292. https://doi.org/10.1126/science.1089134

Eisenberger NI, Taylor SE, Gable SL, Hilmert CJ, Lieberman MD (2007) Neural pathways link social support to attenuated neuroendocrine stress responses. Neuroimage 35:1601–1612. https://doi.org/10.1016/j.neuroimage.2007.01.038

Etkin A, Egner T, Kalisch R (2011) Emotional processing in anterior cingulate and medial prefrontal cortex. Trends Cogn Sci. https://doi.org/10.1016/j.tics.2010.11.004

First MB, Spitzer RL, Gibbon M, Williams JBW (1997) User's guide for the structured clinical interview for DSM-IV axis I disorders SCID-I: clinician version. American Psychiatric Publication, Washington

Fischer G, Ameis N, Parzer P, Plener PL, Groschwitz R, Vonderlin E et al (2014) The German version of the self-injurious thoughts and behaviors interview (SITBI-G): a tool to assess non-suicidal self-injury and suicidal behavior disorder. BMC Psychiatry 14:265. https://doi.org/10.1186/s12888-014-0265-0

Franzen N, Hagenhoff M, Baer N, Schmidt A, Mier D, Sammer G et al (2011) Superior "theory of mind" in borderline personality disorder: An analysis of interaction behavior in a virtual trust game. Psychiatry Res. https://doi.org/10.1016/j.psychres.2010.11.012

Frías Á, Palma C (2015) Comorbidity between post-traumatic stress disorder and borderline personality disorder: a review. Psychopathology. https://doi.org/10.1159/000363145

Groschwitz RC, Kaess M, Fischer G, Ameis N, Schulze UME, Brunner R et al (2015) The association of non-suicidal self-injury and suicidal behavior according to DSM-5 in adolescent psychiatric inpatients. Psychiatry Res. https://doi.org/10.1016/j.psychres.2015.06.019

Hautzinger M, Keller F, Kühner C (2006) Beck depressions-inventar (BDI-II). Harcourt Test Services, Frankfurt

Jamieson JP, Harkins SG, Williams KD (2010) Need threat can motivate performance after ostracism. Pers Soc Psychol Bull 36:690–702. https://doi.org/10.1177/0146167209358882

Kawamoto T, Onoda K, Nakashima K, Nittono H, Yamaguchi S, Ura M (2012) Is dorsal anterior cingulate cortex activation in response to social exclusion due to expectancy violation? An fMRI study. Front Evol Neurosci. https://doi.org/10.3389/fnevo.2012.00011

Leary MR, Springer C (2001) Hurt feelings: the neglected emotion. In: Kowalski RM (ed) Aversive behaviors and relational transgressions. American Psychological Association, Washington, DC

Lis S, Bohus M (2013) Social interaction in borderline personality disorder. Curr Psychiatry Rep. https://doi.org/10.1007/s11920-012-0338-z

Malejko K, Neff D, Brown R, Plener PL, Bonenberger M, Abler B et al (2018) Neural correlates of social inclusion in borderline personality disorder. Front Psychiatry 9:653. https://doi.org/10.3389/fpsyt.2018.00653

Menon V, Uddin LQ (2010) Saliency, switching, attention and control: a network model of insula function. Brain Struct Funct. https://doi.org/10.1007/s00429-010-0262-0

Mitchell JP (2008) Contributions of functional neuroimaging to the study of social cognition. Curr Dir Psychol Sci. https://doi.org/10.1111/j.1467-8721.2008.00564.x

Ochsner KN, Knierim K, Ludlow DH, Hanelin J, Ramachandran T, Glover G et al (2004) Reflecting upon feelings: an fMRI study of neural systems supporting the attribution of emotion to self and other. J Cogn Neurosci. https://doi.org/10.1162/0898929042947829

Perini I, Gustafsson PA, Hamilton JP, Kämpe R, Zetterqvist M, Heilig M (2018) The salience of self, not social pain, is encoded by dorsal anterior cingulate and insula. Sci Rep. https://doi.org/10.1038/s41598-018-24658-8

Powers KE, Wagner DD, Norris CJ, Heatherton TF (2013) Socially excluded individuals fail to recruit medial prefrontal cortex for negative social scenes. Soc Cogn Affect Neurosci 8:151–157. https://doi.org/10.1093/scan/nsr079

Renneberg B, Herm K, Hahn A, Staebler K, Lammers C-H, Roepke S (2012) Perception of social participation in borderline personality disorder. Clin Psychol Psychother. https://doi.org/10.1002/cpp.772

Ruocco AC, Medaglia JD, Tinker JR, Ayaz H, Forman EM, Newman CF et al (2010) Medial prefrontal cortex hyperactivation during social exclusion in borderline personality disorder. Psychiatry Res Neuroimaging. https://doi.org/10.1016/j.pscychresns.2009.12.001

Sebastian CL, Tan GCY, Roiser JP, Viding E, Dumontheil I, Blakemore SJ (2011) Developmental influences on the neural bases of responses to social rejection: implications of social neuroscience for education. Neuroimage. https://doi.org/10.1016/j.neuroimage.2010.09.063

Somerville LH, Heatherton TF, Kelley WM (2006) Anterior cingulate cortex responds differentially to expectancy violation and social rejection. Nat Neurosci. https://doi.org/10.1038/nn1728

Staebler K, Helbing E, Rosenbach C, Renneberg B (2011) Rejection sensitivity and borderline personality disorder. Clin Psychol Psychother 18:275–283. https://doi.org/10.1002/cpp.705

Williams KD, Cheung CK, Choi W (2000) Cyberostracism: effects of being ignored over the Internet. J Pers Soc Psychol 79:748–762

Zetterqvist M (2015) The DSM-5 diagnosis of nonsuicidal self-injury disorder: a review of the empirical literature. Child Adolesc Psychiatry Ment Health. https://doi.org/10.1186/s13034-015-0062-7