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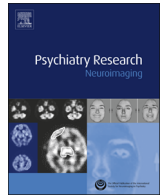
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Dysregulation between emotion and theory of mind networks in borderline personality disorder



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ABSTRACT

Individuals with borderline personality disorder (BPD) commonly display deficits in emotion regulation, but findings in the area of social cognitive (e.g., theory of mind, ToM) capacities have been heterogeneous. The aims of the current study were to investigate differences between patients with BPD and controls in functional connectivity (1) between the emotion and ToM network and (2) in the default mode network (DMN). Functional magnetic resonance imaging was used to investigate 19 healthy controls and 17 patients with BPD at rest and during ToM processing. Functional coupling was analysed. Significantly decreased functional connectivity was found for patients compared with controls between anterior cingulate cortex and three brain areas involved in ToM processes: the left superior temporal lobe, right supramarginal/inferior parietal lobes, and right middle cingulate cortex. Increased functional connectivity was found in patients compared with controls between the precuneus as the DMN seed and the left inferior frontal lobe, left precentral/middle frontal, and left middle occipital/superior parietal lobes during rest. Reduced functional coupling between the emotional and the ToM network during ToM processing is in line with emotion-regulation dysfunctions in BPD. The increased connectivity between precuneus and frontal regions during rest might be related to extensive processing of internal thoughts and self-referential information in BPD.

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1. Introduction

Current theories of borderline personality disorder (BPD) propose that the experience of early life trauma (e.g., childhood abuse or maternal separation), genetics, neurobiological alterations, or a combination of the above may play crucial roles in the development of the disorder (Goodman et al., 2004; Steele and Siever, 2010). In recent years, the spotlight has increasingly been focused on neurobiological abnormalities revealed using in vivo neuroimaging techniques. This focus has resulted in a growing body of evidence supporting the existence of functional neurobiological disturbances in BPD (Goodman et al., 2004; Foti et al., 2011). The majority of previous functional magnetic resonance imaging (fMRI) studies in BPD have looked at activation abnormalities in regions understood to be involved in the regulation of stress responses, emotion and affect, amongst others. The most common finding amongst these studies is that of hyperactivity in

the amygdala and insula of BPD patients as well as decreased frontal activity, e.g., in the anterior cingulate cortex (ACC), compared with controls during tasks that involve the processing of emotionally aversive stimuli (Donegan et al., 2003; Minzenberg et al., 2007; O'Neill and Frodl, 2012; Krause-Utz et al., 2014).

Social cognitive aspects like mentalization and theory of mind (ToM), although relevant to BPD and its therapy, have thus far only been explored at a rudimentary level in BPD research. ToM describes the ability an individual has to understand and appreciate that others can have mental states (wants, needs, beliefs, knowledge, emotions, etc.) different from one's own, and to understand that these can be used to explain and predict the behaviours of others (Saxe and Kanwisher, 2003). *Mentalization* is the process by which we implicitly and explicitly interpret the actions of ourselves and others as meaningful on the basis of intentional mental states (Bateman and Fonagy, 2004), and thus mentalization shares similarities with the concept of ToM. A deficit in this ability is found in a number of psychiatric and neurodevelopmental disorders, BPD being no exception (Bouchard et al., 2010). Amongst individuals with BPD, researchers have suggested that a deficit in cognitive empathy may contribute to the

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interpersonal dysfunction typically observed (Harari et al., 2010). Franzen et al. (2011) used the trust game to analyse processes of mentalising in a simulated social interaction situation. BPD patients adjusted their investment to the fairness of their partner. In contrast, healthy controls disregarded the trustees' fairness in the presence of emotional facial expressions. Both groups performed equally in an emotion-recognition task and assessed the trustees' fairness comparably (Franzen et al., 2011). When the unfair trustee provided emotional cues, BPD patients assessed their own behaviour as more fair, while the lack of cues led patients to assess their own behaviour as unfair. The authors thus concluded that BPD patients are superior in the attribution of mental states to interaction partners when emotional cues are present (Franzen et al., 2011).

With regard to functional neuroimaging studies, no pure ToM tasks have yet been used. Studies on social cognition in BPD, which involve aspects of ToM, but also have wider implications on encoding, storage, retrieval, and processing of information about other individuals, have found ambiguous results. At present there are two studies in patients with BPD addressing the issue of altered social cognition processing during fMRI. Using the Multifaceted Empathy Test (MET), one study found evidence suggesting deficits in both emotional and cognitive empathy in BPD (Dziobek et al., 2011). Since subjects are required to infer the mental states of the individuals shown in the photographs by selecting one of four mental state descriptors, this task involves some aspects of ToM. Applying the fMRI version of the MET, the authors found that during emotional empathy, the right mid-insula was more activated in individuals with BPD than in non-clinical controls (Dziobek et al., 2011). During cognitive empathy processing, however, the BPD sample displayed decreased activation in both left superior temporal sulcus (STS) and gyrus (STG) (Dziobek et al., 2011). The insula is thought to be related to self-oriented emotion processing (Wicker et al., 2003; Jabbi et al., 2007; Craig, 2009; Singer et al., 2009), and the STS and STG are related to the ability to infer the mental states of others (Saxe and Wexler, 2005; Dodell-Feder et al., 2011).

A paradigm with three social cognition tasks, differing in their complexity – basal processing of faces with a neutral expression, recognition of emotions, and attribution of emotional intentions (affective ToM) – was applied in the other study. BPD patients showed no deficits in social cognition on the behavioural level. However, while the control participants showed increasing activation in areas of the social brain with increasing complexity in the social-cognitive task, BPD patients had *hypoactivation* in these areas and *hyperactivation* in the amygdala, effects that were not modulated by task complexity. From this activation pattern, the authors concluded that there is an enhanced emotional approach in the processing of social stimuli in BPD that allows good performance in standardised social-cognitive tasks, but might be the basis of social-cognitive deficits in real-life social interactions (Mier et al., 2013).

While there are no studies in BPD using ToM tasks, ToM was investigated in healthy participants. With fMRI, findings in 12 participants who performed the classic attribution task (McArthur, 1972) showed that the left medial prefrontal cortex (MPFC) played a significant role in ToM (Harris et al., 2005). However, this finding has not proved to be consistent. Saxe and Wexler (2005) found that enhanced activation in the right temporo-parietal junction was selective to the attribution of mental states, and was not recruited by processing other socially relevant facts about a person. Further, right temporo-parietal junction activity was enhanced when the protagonist of a story professed a belief or desire that was inconsistent with the subject's expectations, based on the protagonist's background (Saxe and Wexler, 2005). These results are consistent with neuropsychological deficits in patients with selective forms of brain

damage. Damage to the right temporo-parietal junction is associated with a selective impairment of ToM, whereas damage to the medial prefrontal cortex is not (Saxe and Wexler, 2005). A within-subject comparison of reorienting and ToM paradigms revealed that both paradigms activated very similar temporo-parietal junction regions (Mitchell, 2008) implying that the temporo-parietal junction is also involved in non-social mental processes. Interestingly, another study suggested that there are neighbouring but distinct regions within the right temporo-parietal junction implicated in ToM and orienting attention (Scholz et al., 2009).

One option when investigating ToM processes is to use humorous material based on false beliefs of others. It has recently been shown that ToM cartoons (which require additional mentalising skills in order to be understood – the ability to recognise that one character portrayed in the cartoon has a false belief – require more involvement of so-called 'mentalising areas' [e.g., medial prefrontal cortex, temporo-parietal junction (TPJ)] in contrast to cartoons that can be understood without taking the characters' false beliefs into account (Samson et al., 2008, 2009). While there is a good understanding on which regions are activated during ToM processes, no study has investigated the functional connectivity during ToM processing in BPD patients compared with controls.

Work considering "functional connectivity" amongst neural networks is also less common in the BPD literature. As we use the term here, functional connectivity describes the relationship between different brain regions and within particular networks by assessing the correlation of their neuronal activity (Nierhaus et al., 2012). Regions within one particular neural network, the default mode network (DMN), have been found to display their greatest levels of activity when at rest, and decreased activity in some DMN sub-regions during task-based stimulation (Sheline et al., 2010; Zhang and Li, 2012b). During these periods of "active rest", the DMN is thought to be involved in internal processes such as self-referential processing, inner speech, emotional control, episodic memory, and ToM processes (Spreng et al., 2009; Wolf et al., 2011). Research has shown the constituent regions of the DMN to include the medial temporal lobe, the medial prefrontal cortex, the posterior cingulate cortex, the precuneus, and the medial, lateral, and inferior parietal cortex (Broyd et al., 2009; Spreng et al., 2009; Wolf et al., 2011). Surprisingly, though interest in the DMN is on the rise generally, and given the correspondence between the DMN functional roles and the dysfunction observed in BPD, there remains a dearth of research investigating abnormalities in DMN functioning in BPD. Of the research that exists, one study explored alterations in the functional connectivity of the DMN in patients with BPD during pain processing. This particular study observed less integration of the left retrosplenial cortex and left superior frontal gyrus into the DMN in the BPD group than in the controls during pain appraisal (Kluetsch et al., 2012). An earlier study explored prefrontal and limbic resting state networks in BPD patients without any external stimulus. To our knowledge, it is the only study thus far to explicitly examine DMN connectivity in BPD, yielding results that showed an increase in functional connectivity in the left inferior frontal gyrus (IFG) and the left insula, and decreased connectivity in the left cuneus in the BPD group (Wolf et al., 2011). The researchers opine that, with regard to the increased connectivity observed in the IFG, these findings may have implications for the processing of internal thoughts, self-referential information, and interpersonal interactions, and may in the future be found to be a potential biological marker for the disorder (Wolf et al., 2011). Regarding the increased connectivity with the insula, the researchers suggest that abnormal connectivity may be related to both dissociative symptoms and decreased pain sensitivity observed in BPD patients (Wolf et al., 2011).

In the current study, the overall aims were twofold. The first portion of the study investigated whether a dysfunction in connectivity during ToM processing could be found between emotional network, in particular the anterior cingulate cortex (ACC), and ToM regions in BPD patients compared with healthy controls. The ACC was chosen as the seed region as it is known to be involved in emotion processing, empathy, and cognition (Vollm et al., 2006; Bush et al., 2000; Ruocco et al., 2013), with previous studies observing divergent neural dynamics in the ACC of BPD patients compared with healthy controls (Dziobek et al., 2011; Ruocco et al., 2013). Moreover, the ACC has an important role in the integration of neuronal circuitry for affect regulation. As a result, it has been identified as an important region in the study of the psychopathology of various disorders typified by emotion dysregulation (Stevens et al., 2011). Furthermore, the ACC is known as a good seed region to investigate the affective network (Sheline et al., 2010; McCarthy et al., 2013). The second part of the study addressed the gap in research on the DMN in BPD patients by mapping the functional connectivity corresponding to the precuneus seed region within the DMN in a sample of BPD patients compared with healthy controls during resting state.

2. Methods

2.1. Participants

As BPD is much less frequently found in men (75% of those with the disorder are women (Oldham, 2004)), it was decided that the participant group would consist solely of women to avoid potential gender-based differences. The BPD patient group ($n=22$) were receiving continuous treatment from the South-West mental health services in Dublin. The BPD participants were well known to the service and were mainly treated with outpatient and home care, and with crisis admission when necessary. The participants were only further interviewed for suitability for the study once the continuous care consultant indicated these inclusion criteria had been met. Diagnosis according to DSM-IV was thus confirmed by a second specialist in psychiatry. A cohort of 19 healthy female volunteers matched for age (30.1 years (S.D.=8.0)), was recruited from the local community. For this controls were recruited from the same local community as the patients by contacts via service staff. The volunteers and patients were carefully screened for medical conditions to ensure that none had a personal history of neurological disorder, severe medical illness, head injury, and alcohol or substance dependency. Healthy participants were excluded if they had a personal history of any psychiatric disorder (Axis I or Axis II; American Psychiatric Association, 1994). In addition, healthy controls were not allowed to have any psychiatric disorder. Demographic variables and inclusion and exclusion criteria were assessed in all participants using a standardised questionnaire and through structured interview based on the Structured Clinical Interview for DSM-IV Patient Version (SCID-I) by registered psychiatrists. Two patients had not completed the assessment sessions. Three patients had to be excluded from fMRI analysis due to excessive movement during the scanning session. The cut-off point chosen for this purpose was a head movement of 3 mm in any direction, which relates to the size of one voxel used in the functional analysis.

Thus, 17 patients with BPD and 19 healthy controls entered the fMRI analysis (Table 1). Of the 17 patients, 12 were taking selective serotonin reuptake inhibitors or dual acting antidepressants (venlafaxine or duloxetine) at the time of investigation. Of these, three additionally were receiving quetiapine and one olanzapine.

Ethical approval for the study was obtained from the Adelaide and Meath Hospital and St. James's Hospital, Dublin, Ireland ethics committee. All participants were given detailed oral and written information and had to sign an informed consent form before participating in the study.

2.2. Psychometric assessment

The rating scales used for this study in addition to the SCID-I were the Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960) and the Beck Depression Inventory (BDI-II) (Beck et al., 1988). Moreover, the Eysenck Personality Questionnaire (Eysenck and Eysenck, 1964) and the Barratt Impulsiveness Scale (Patton et al., 1995) were used.

2.3. fMRI task

The stimulus material consisted of two types of cartoons, visual puns (PUN) and jokes requiring mentalising (TOM), as well as a control condition that consisted of non-humorous pictures containing an incongruity that could not be resolved meaningfully (INC). All pictures were low in aggressive, violent, and sexual content and were validated by use in previous studies (Samson et al., 2008, 2009). To investigate brain activity during resting state trials, these cartoon trials were interleaved with rest events (NULL) during which participants observed a blank screen. All participants processed a total of 120 trials (30 INC+30 PUN+30 TOM+30 NULL). Stimuli were presented every 10 s on average and with variable stimulus-onset delays (0, 400, 800, 1200 or 1600 ms). Each stimulus was presented for 6000 ms during which participants were instructed to make a response. Below each picture (cartoon), the word "understood" was printed on the left side and the words "not understood" were printed on the right side. Participants were asked to press the corresponding button (left/right) with their index or middle finger, respectively, depending on whether they understood the joke. Only those trials were used for analyses in which participants pressed the button in time. Thus, all the trials that participants had responded to, regardless of whether they had understood or not understood the cartoon, were taken into account for the fMRI analysis. The fMRI task took about 18 min.

2.4. MRI data acquisition

Magnetic resonance images were obtained with a Philips Achieva MRI scanner (Philips Medical System, Netherland BV, Veenphuis 4-6, 5684 PC Best, The Netherlands) operating at 3 T. For the cognitive paradigm run, 26 axial slices (3.5 mm × 3.5 mm × 3.5 mm resolution, 0.75 mm spacing), parallel to the anterior-posterior commissure plane and covering the whole brain were acquired using a single shot, gradient recalled echoplanar imaging sequence (repetition time=2000 ms, echo time=30 ms, 90° flip angle). One functional run with 620 time points was acquired, with each time point sampling over the 26 slices. Before the functional run, 180 anatomical slices T₁-weighted 3D-MPRAGE sequence (repetition time=11.0 ms, echo time=4.4 ms, total acquisition time=7 min 30 s, number of acquisitions=1; field of view=250 mm × 256 mm × 160 mm, matrix=256 mm × 256 mm, resolution=0.9 mm × 0.9 mm × 0.9 mm) with the same spatial orientation as when the functional data were acquired.

Table 1

Demographic and clinical data for patients with borderline disorder (BPD) and healthy controls.

	BPD patients	Controls	Statistics
Age	31.4 ± 9.5	29.3 ± 7.5	N.S.
Height	165.2 ± 6.2	168.0 ± 5.3	N.S.
Weight	71.6 ± 14.7	60.7 ± 8.3	$t=2.64$; d.f.=22.2; $p < 0.05$
Cigarette consumption	11.7 ± 11.1	1.5 ± 3.6	$t=3.45$; d.f.=17.6; $p < 0.005$
Alcohol units per week	4.1 ± 7.7	3.4 ± 3.7	N.S.
Education	2.5 ± 0.72	2.88 ± 0.33	$t=-1.71$; d.f.=9.8; $p < 0.05$
HDRS	24.31 ± 10.3	0.37 ± 0.76	$t=8.5$; d.f.=15.4; $p < 0.001$
BDI-II	41.63 ± 10.13	4.26 ± 3.60	$t=14.01$; d.f.=18.2; $p < 0.001$
BIS total	79.56 ± 7.21	62.63 ± 7.1	$t=6.98$; d.f.=33; $p < 0.001$
EPQ-Neuroticism	10.52 ± 1.37	3.63 ± 2.73	$t=9.71$; d.f.=27.2; $p < 0.001$
EPQ-Extraversion	4.47 ± 3.9	9.42 ± 3.16	$t=-4.2$; d.f.=33; $p < 0.001$

Note: shown are means and S.D. (±). The level of education was measured in three categories where 1=no completed secondary level education, 2=secondary education, 3=third level education. Abbreviations: N.S.: Nonsignificant; EPQ: Eysenck Personality Questionnaire; HDRS: Hamilton Depression Rating Scale; BDI: Beck Depression Inventory; BIS: Barrett Impulsivity Scale.

2.5. SPM8 pre-processing

Using SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm8>) data were pre-processed with the following steps: (1) compensation of systematic, slice-dependent time shifts; (2) elimination of systematic odd-even slice intensity differences due to interleaved acquisition; and (3) rigid body correction for interframe head motion within and across runs. Data were excluded if motion parameters exceeded 3 mm in any direction or 3.0° of any angular motion throughout the course of the scan. Next, co-registration of the structural T1 image to the functional scans was carried out. Spatial normalisation to standard 3 mm × 3 mm × 3 mm Montreal Neurological Institute space was then applied to the functional images and to the structural image, respectively, to allow for inter-subject analysis. Functional resting state data were then spatially smoothed (smoothing full width at half-maximum=8 mm).

2.6. Connectivity analyses

The CONN resting state software (<http://www.nitrc.org/projects/conn/>) performs seeded voxel correlations by estimating maps showing temporal correlations between the blood level oxygenation dependent (BOLD) signal from given seed and that at every brain voxel. The toolbox implements a *CompCor* strategy for physiological noise source reduction, first level General Linear Model for correlation and regression connectivity estimation, and second level random-effect analyses.

Using CONN resting state software, the data were temporally band-pass filtered ($0.009 < f < 0.08$). Several sources of spurious variance along with their temporal derivatives then were removed from the data by linear regression, such as signal from regions centred in the white matter, cerebrospinal fluid, movement and effects of rest. This regression procedure removes fluctuations unlikely to be involved in specific regional correlations. The conditions were also entered so that it is possible to calculate functional coupling within the conditions, e.g., within the null condition or within the ToM condition.

2.7. Functional coupling analysis

To compute functional connectivity maps corresponding to a selected seed region of interest (ROI), the regional time course was correlated against all other voxels within the brain (Bokde et al., 2006). As they were not relevant to the present research question, the connectivity within the PUN and INC trials was not calculated, and only ToM and NULL trials were further considered. Correlation maps were produced by extracting the BOLD time course from a seed region (10-mm sphere each), and then computing the correlation coefficient between that time course and the time course from all other brain voxels. Based on data from previous connectivity studies (Fox et al., 2006; Sheline et al., 2010; McCarthy et al., 2013), the left and right subgenual anterior cingulate cortex (ACC; $\pm x=10$, $y=35$, $z=2$) was extracted as the seed region of interest from the affective network that was modulated between ToM trials and NULL events; and the left and right precuneus ($\pm x=7$, $y=-60$, $z=21$) as the seed region of interest in the DMN during NULL events. Thus, the DMN was modulated during rest (NULL events) and the ToM network was modulated by functional variation in ToM and NULL events. The principal techniques used were computation of whole brain, voxel-wise intrinsic functional connectivity maps.

2.8. Statistical analysis

To test differences of clinical and demographic data between groups, we used in SPSS version 21. All *t*-test comparisons were made after checking the variables homogeneity of variance (d.f. were adjusted where necessary, Table 1).

We analysed resting-state fMRI data to determine significant differences in functional connectivity between BPD and control participants. Age and BDI depression scores were used as covariates. In an additional analysis, current medication (none, antidepressants, antidepressants+antipsychotics) was also used as a covariate to control for medication effects. Since depression scores may present part of the symptoms of BPD, which were of interest, we also analysed the data without covarying for BDI. A family-wise error (FWE), whole brain corrected threshold was reduced to $p < 0.025$ from $p < 0.05$ because the connectivity was analysed within the two different networks. Moreover, mean connectivity data were extracted from areas that showed significant differences between patients and healthy controls. The anatomic localisation of significant clusters was identified using the AAL toolbox (Tzourio-Mazoyer et al., 2002).

3. Results

3.1. Demographic and clinical variables

Patients with BPD showed significantly higher impulsivity scores as measured with the BIS, higher depression scores, higher

neuroticism and lower extraversion compared with healthy controls. Age, height and alcohol consumption did not differ between groups. As expected, patients with BPD consumed significantly more cigarettes and fewer patients with BPD were able to attend third level schools (Table 1).

3.2. Behavioural data

No significant differences ($p > 0.05$) were found for the overall number of responses made ($t=1.15$), subtotal of positive responses (“understood”; $t=0.36$), and the subtotal of negative responses (“not understood”; $t=0.94$). The total number of responses between patients and healthy controls was not different under the ToM condition. However, when distinguishing between positive and negative responses, patients were less likely to respond “understood” under the ToM condition ($M_{BPD}=15.6$, $S.D._{BPD}=5.0$, $M_{HC}=20.1$, $S.D._{HC}=5.0$, $t=-2.58$, and $p < 0.05$) than controls.

Differences in mean response times were no significant between patients and healthy controls across all conditions combined ($t=1.85$, $p > 0.05$) and also within the ToM condition ($t=1.46$, $p > 0.05$). When discriminating between positive (understood) and negative (not understood) responses, the pattern of differences became more sophisticated. Patients with BPD took longer for positive responses across all conditions than did healthy controls within the ToM condition ($t=2.37$, $p < 0.05$).

3.3. Affective network-ToM interactions

During the ToM and NULL conditions, decreased functional connectivity was found for patients compared with controls between ACC (seed) and three brain areas: the left superior temporal cortex (STS), right mid-cingulate cortex (MCC), and right supramarginal/inferior parietal (TPJ) (Fig. 1, Table 2).

3.4. Default mode network

After visual inspection of the resting state network, the differences between patients and controls were calculated. The resting state network for all participants ($N=36$, Fig. 2), with right precuneus used as the seeding region, showed a standard DMN



Fig. 1. Connectivity changes in the theory of mind network between patients with BPD and healthy controls. Decreased functional connectivity between ACC (seed) and right TPJ and right MCC was found in BPD compared with healthy controls. Activation maps are superimposed on a 3D standardised template in caudal view. The right hemisphere is depicted on the right.

Table 2

Connectivity changes between BOLD response in the emotional region ACC and the whole brain during ToM processing for patients < healthy controls for [ToM–NULL].

K	FWE _{cluster}	Region	FWE _{voxel}	t	Coordinates (mm)		
					x	y	z
603	0.001	L Sup. Temporal	0.016	6.09	–60	–4	–2
		L Sup. Temporal	0.192	5.05	–60	4	–5
		L Sup. Temporal	0.486	4.57	–42	–35	22
1507	< 0.001	R Mid. Cingulum	0.070	5.49	14	–26	40
		R Mid. Cingulum	0.203	5.03	10	–20	35
		R Mid. Cingulum	0.241	4.95	10	–40	50
844	< 0.001	R Supramarginal	0.072	5.48	66	–32	36
		R Supramarginal	0.134	5.21	58	–32	40
		R Inf. Parietal	0.326	4.79	52	–35	45

Note: seed region: anterior cingulate cortex. FWE cluster corrected. Shown are also FWE voxel-corrected *p*-values, *t*-values as well as coordinates in Montreal Neurological Institute space.

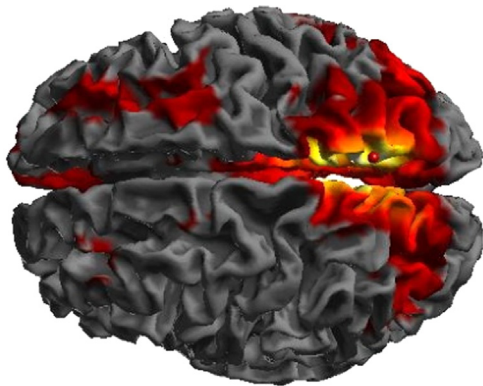


Fig. 2. Connectivity in the default mode network displayed for all participants. The precuneus was used as seed region. Functional connectivity is superimposed on a 3D standardised template. Right hemisphere is seen on the top and left hemisphere on the bottom.

Table 3

Default mode network: connectivity changes between BOLD response in the precuneus and the whole brain during rest for patients > healthy controls.

K	FWE _{cluster}	Region	FWE _{voxel}	t	Coordinates (mm)		
					x	y	z
259	0.067	L Inf. Frontal Operculum	0.025	5.98	–42	14	16
		L Inf. Frontal Triangularis	0.350	4.72	–48	18	20
		L Inf. Frontal Triangularis	0.535	4.36	–38	22	16
401	0.014	L Precentral	0.137	5.17	–42	10	48
		L Mid. Frontal	0.335	4.72	–48	6	52
		L Precentral	0.915	3.95	–42	2	44
384	0.016	L Mid. Occipital	0.674	4.31	–24	–64	40
		L Sup. Parietal	0.888	4.01	–22	–74	54
		L Precuneus	0.913	3.95	–8	–74	54

Note: seed region: precuneus. $P < 0.05$, FWE cluster corrected. Shown are also FWE voxel corrected *p*-values, *t*-values as well as coordinates in Montreal Neurological Institute space.

pattern. Increased functional connectivity was found in patients compared with controls between precuneus (seed region) and three brain areas which were located: left inferior frontal gyrus (IFG), left precentral/middle frontal, and left middle occipital/superior parietal (Table 3, Fig. 3).

In both the DMN and the affective network-ToM interaction, use of medication status as a covariate did not change the results. Also, additional analysis without using BDI as covariate did not change the results.

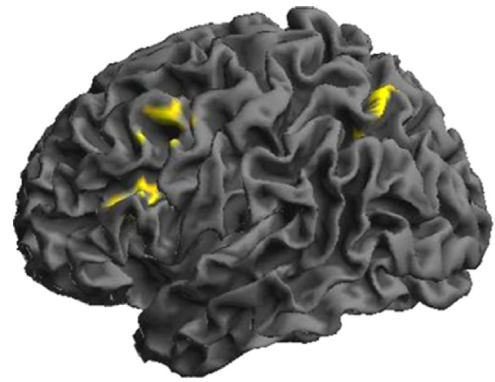


Fig. 3. Connectivity changes in the default mode network between patients with BPD and healthy controls. Patients showed significantly increased functional connectivity than healthy controls between the precuneus (seed) and the left inferior frontal gyrus, left precentral, left midfrontal, left midoccipital and left superior parietal cortices. Activation maps are superimposed on a 3D standardised template. View is on the left hemisphere.

4. Discussion

The main finding of the present study was of decreased functional connectivity of the seed emotional region, the subgenual ACC, with the left STS, right TPJ and MCC in BPD patients compared with controls. While the MCC has been shown to be involved in both self- and other-perspectives (Vogt, 2005), the bilateral STS and TPJ belong to the core neural network of mentalising (Saxe and Wexler, 2005; Dodell-Feder et al., 2011). These latter two areas make up the network described by the cognitive neuroscience term “temporo-parietal junction” (TPJ), known collectively to play a crucial role in self-other distinction processes, ToM, and the ability to make moral decisions (Saxe and Kanwisher, 2003). The right TPJ, in particular, includes areas that might be recruited exclusively by mentalising (Saxe and Pelphrey, 2009; Scholz et al., 2009). Regions included in the ToM network shown in fMRI studies are the left and right TPJ, precuneus and medial PFC (Scholz et al., 2009). Goel and Dolan (2001, 2007) also found affective brain areas, namely the ventromedial prefrontal cortex (VMPFC) and the subcortical nucleus accumbens, along with the aforementioned network (TPJ and STS), to play a role in ToM. In this context, our data indicate a dysconnectivity between the affective brain region, i.e., the subgenual ACC, and the ToM network in BPD patients compared with healthy controls and thus a dysfunctional or even a lack of modulation of the ToM network from regions involved in emotion processing. It is understandable that during ToM emotional processes such as mentalising about emotions also take place. During ToM tasks, the ACC was also found to be active, but information processing related to a third person consistently involved the dorsal part of the ACC and not the subgenual part of the ACC. This fact, the use of cartoons that, e.g., did not involve emotional faces and the knowledge that emotional regulation is altered in BPD support the notion of dysconnectivity between ACC and ToM regions (Apps et al., 2012; Lisofsky et al., 2014).

Interestingly, patients with BPD indicated less ToM trials as being “understood” than did healthy controls, and they also took longer to respond that they had understood ToM trials. Thus, it seems that they were more doubtful and unsure about the interpersonal content of the ToM stimuli. This observation seems to be in line with BPD symptomatology, as trust is one issue in interpersonal problems. In conjunction with the previous findings of Dziobek et al. (2011), both behavioural and fMRI data would in turn provide a basis for the theory that many difficulties faced by patients with BPD arise from an inability to use their ToM capacities in an efficient and balanced way. In a meta-analysis by Ruocco et al. (2013) Ruocco et al., decreased activity in the ACC of a

sample of BPD patients compared with healthy controls was noted. Considering the ACC's role in affect regulation, and the roles of the MCC and TPJ in ToM processes, a dysfunctional connection between their respective networks could potentially reflect the dysregulation of emotions during social cognitions in BPD. Interestingly, the ACC has repeatedly been found to display increased activity in functional studies of MDD (Mayberg et al., 2005; Savitz and Drevets, 2009; Fan et al., 2013), and thus ACC coupling seems to distinguish BPD from mood disorders. In addition to this, studies of functional connectivity in MDD have also shown decreases in resting state coupling between the ACC network and the amygdala, medial temporal lobe, and areas of the frontal and prefrontal cortices (Davey et al., 2012; de Kwaasteniet et al., 2013; Pannenkoek et al., 2014). These findings of task-based and resting state ACC functional and coupling abnormalities in MDD, in comparison with those of the current study and previous research, appear to distinguish BPD from mood disorders, at least in relation to ACC function.

The second network investigated in the present study was the default mode network (DMN), studied during resting conditions. The only study that has attempted this in BPD is recent work by Wolf et al. (2011) who, similarly to the present study, found increased connectivity in BPD between precuneus and left IFG, also using a similar method. In particular, the comparison of functional connectivity during rest revealed higher connectivity in BPD patients between the precuneus in areas that are not generally included in the DMN like the left IFG, left middle frontal, and left middle occipital/superior parietal cortex. The initial conclusion that may be drawn from this finding is that in BPD the DMN is altered, perhaps including different regions in its baseline functioning than in controls. The precuneus was chosen as a region of interest as previous research has suggested it to play a crucial role in the DMN, with involvement in reflective, self-related processing, empathy, awareness and conscious information processing, and episodic memory, amongst other things (Vollm et al., 2006; Fransson and Marrelec, 2008; Zhang and Li, 2012a). While there was no decrease in connectivity from the precuneus to any brain area, patients displayed higher connectivity to the left IFG (comprising Brodmann areas 44 and 45, which together are known as Broca's area), left mid-frontal, left precentral, and left mid-occipital/superior parietal regions compared with healthy controls. This increased connectivity between the precuneus and the left frontal regions may have implications in terms of extensive processing of internal thoughts and self-referential information in BPD. The DMN processes related to other processes, such as ToM, involved during rest (Spreng et al., 2009; Wolf et al., 2011) seem not to be responsible for this increased connectivity, since we were able to show a decreased connectivity between ACC and typical ToM regions in the present study. However, conclusions about whether there are more alterations in self-referential or processes related to others, or whether these changes are related to inner speech, would be premature at this stage. This hypothesis, however, could be tested in future studies by investigating true "task-negative" resting state connectivity, and contrasting it with the connectivity during a cognitive task that involves processing of language or ToM.

In terms of the practical limitations of the methodology, we must look to past studies. The majority of past positron emission tomography (PET) functional studies examined patients only during the resting state, with results producing very little consistency (O'Neill and Frodl, 2012). One reason for the lack of consistency amongst these PET studies could be that during the resting state the patient's emotional state is not known, and thus the range of neural activity could be vast, especially with a patient sample typified by emotional fluctuations. Whereas in past studies, which generally involved specific tasks or images, the patients' emotional states could be more accurately predicted and thus the resulting images

compared with more reliability (O'Neill and Frodl, 2012). This would suggest that when investigating neurobiological functioning in BPD patients, studies that use specific emotion-related stimuli provide a more reliable measure than resting state studies (O'Neill and Frodl, 2012). This may hold true for DMN functional connectivity studies in BPD as well, and it is important to be aware of whilst interpreting any results both in the present study and in future studies.

Functional magnetic resonance imaging measures the blood level oxygenation dependent (BOLD) signal and does not measure neuronal activity directly. Thus, changes in BOLD signals may not reflect altered information processing, if there are differences in neurovascular coupling. Thus fMRI studies should control for differences in blood oxygenation or in breathing. Differences in head movements might also form a part and in functional connectivity. Motion-related artifacts are thought to affect functional connectivity/time course data in resting state functional connectivity studies (Power et al., 2012). In the present study there was no difference in head motion between groups with BPD and healthy controls. Another general limitation is also that brain function is influenced by micro-fluctuations that are independent of task or no-task conditions. Reassuring is that the results of the present study show clearly areas involved in ToM activity, and thus the task modulated these areas and their connectivity.

Given the similarity in symptomology observed between the two disorders, research methodologies in BPD have often followed those of post-traumatic stress disorder (PTSD). It has been suggested that DMN connectivity may have potential as a predictor of PTSD symptom severity in acutely traumatised subjects (Lanius et al., 2010). In an attempt to explore the potential of the above-mentioned dysconnectivity as a biological marker for BPD, it is recommended that future studies should also carry out functional connectivity analyses in the most commonly documented comorbidities of BPD, which are MDD, attention deficit hyperactivity disorder (ADHD), and PTSD. PTSD is of particular interest given that both BPD and PTSD are highly related to experiences of trauma (Zetzsche et al., 2006; Pagura et al., 2010; Philippsen et al., 2010; Stein et al., 2010), and many common neurobiological abnormalities have been identified between the two (O'Neill et al., 2013). Although MDD was the only comorbidity that was allowed in our BPD sample, which increased the homogeneity of the sample, this in itself may limit the generalisability of the findings given the high occurrence of other/additional comorbidities found in the wider population of individuals with BPD. To minimise the impact of depression on our results, we used depression severity as a covariate in the analyses. No additional standardised questionnaires were used to confirm the diagnosis of BPD apart from the DSM-IV criteria, which could be seen as a limitation. However, the BPD diagnosis was based on our long-term and continuous clinical management of these patients in our psychiatric service and confirmed by an additional consultant in psychiatry.

An additional avenue for future research may lie in further study of the sub-regions of the precuneus and their role in DMN function, specifically within BPD. Zhang and Li (2012a) recently provided evidence for different roles in eight sub-regions of the precuneus. Thus, examining the precuneus as a whole may lead to distorted data as other studies have observed positive connectivity with the DMN for ventral but not dorsal precuneus (Buckner et al., 2008; Zhang and Li, 2012a).

The investigation of DMN connectivity within resting conditions from a mixed blocked event-related design needs also to be viewed with caution. Although it was described that there are many similarities within a continuous resting state connectivity and that this can be obtained from a block design or a mixed blocked event-related design (Fair et al., 2007), our DMN connectivity analysis cannot be seen as identical to continuous resting state fMRI. In the present study we used 30 rest periods of 10-s duration, whereas rest periods in the study by Fair et al. were longer: 30 s. Inclusion of medication use in

this sample of patients with BPD has to be considered as a potential limitation, since 12 of the 17 patients included were on antidepressants and four additional patients were on antipsychotics. It is known that anti-depressants can affect brain function (Frodl et al., 2011; Samson et al., 2011). However, using medication status (none, antidepressant, antidepressant+antipsychotic) as an additional covariate did not change the results, arguing against a huge medication effect. The question of whether treated patients and patients with BPD with psychiatric comorbidities should be excluded to homogenise clinical sample characteristics remains controversial, and such an exclusion might focus on an atypical group of BPD patients (Lis et al., 2007). As expected, patients with BPD age matched with controls had completed fewer school years. However, although it is worth noting that the difference may be a reflection of an above average level of education amongst the healthy participants in this study, such an educational gap is not out of keeping with previous large-scale research (Zanarini et al., 2007). Symptoms of BPD usually first appear during childhood and adolescence, although they are not usually diagnosed as such at that time. The early emergence of symptoms of BPD can impact on the social and personal development of the individual, and consequently also affect the likelihood and ability of these individuals to pursue higher levels of education (Sodian and Frith, 2008). Thus, it is possible that the education difference in an age-matched cohort may reflect the burden of the disorder, whilst a sample matched with respect to level of education could result in sample bias. Conversely, there is also reason to believe that level of education may impact individual performance on ToM tasks, contradicting the current findings (Li et al., 2013). This complex and as yet undefined relationship between level of education and ToM ability makes it difficult to fully discern the affecting factors, and is a limitation of the present study. To address this in the future, a solution may be to match for level of parental education across the sample.

A promising finding is the reduced functional coupling between the ACC as a seed region for the emotional network and the ToM (mentalising) network indicating dysregulation between these two networks in line with emotion-regulation dysfunctions in BPD. Moreover, higher resting state functional connectivity is also of interest since it may be linked to higher arousal in BPD, a topic that needs to be investigated further in future studies.

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