Published in final edited form as:

Arch Gen Psychiatry. 2012 October ; 69(10): 993–1002. doi:10.1001/archgenpsychiatry.2012.476.

Alterations in default mode network connectivity during pain processing in borderline personality disorder

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Abstract

Context—Recent neuroimaging studies have associated activity in the default mode network (DMN) with self-referential and pain processing, both of which are altered in borderline personality disorder (BPD). In patients with BPD, antinociception has been linked to altered activity in brain regions involved in the cognitive and affective evaluation of pain. Findings in healthy subjects indicate that painful stimulation leads to blood oxygenation level-dependent (BOLD) signal decreases and changes in the functional architecture of the DMN.

Objective—To connect the previously separate research areas of DMN connectivity and altered pain perception in BPD and explore DMN connectivity during pain processing in patients with BPD.

Design—Case-control study

Setting—A university hospital

Participants—Twenty-five women with BPD, 92 percent with a history of self-harm, and 22 age-matched controls.

Interventions—Psychophysical assessment and functional MRI (fMRI) during painful heat versus neutral temperature stimulation.

Main Outcome Measure—DMN connectivity as assessed via independent component analysis and psychophysiological interaction analysis.

Results—Compared to controls, patients with BPD showed less integration of the left retrosplenial cortex and left superior frontal gyrus into the DMN. Higher BPD symptom severity and trait dissociation were associated with an attenuated signal decrease of the DMN in response to painful stimulation. During “pain” versus “neutral”, BPD patients exhibited less posterior cingulate cortex seed region connectivity with the left dorsolateral prefrontal cortex.

Conclusion—Patients with BPD showed significant alterations in DMN connectivity, with differences in spatial integrity and temporal characteristics. These alterations may reflect a different cognitive and affective appraisal of pain as less self-relevant and aversive, and a deficiency in the switching between baseline and task-related processing. This deficiency may be related to everyday difficulties of BPD patients to regulate their emotions, focus mindfully on one task at a time, and efficiently shift their attention from one task to another.

Background

Patients with borderline personality disorder (BPD) frequently experience stress-induced aversive states of inner tension and dissociation,^{1,2} which are often associated with analgesia and self-injurious behavior (SIB).^{3,4} Specifically, many patients with BPD engage in SIB to regulate affect, decrease dissociation and regain awareness of physical sensations.⁵⁻⁷ Experimental studies confirm reduced pain sensitivity in patients with BPD under stress and

non-stress conditions, which cannot be explained by sensory-discriminative or attentional factors.⁸⁻¹⁰ Instead, findings from pain research using a thermal stimulation paradigm suggest that BPD patients show altered activity in brain regions implicated in the cognitive and affective evaluation of pain.^{11,12} Compared to healthy controls (HC), BPD patients displayed increased activation in the dorsolateral prefrontal cortex (DLPFC) coupled with deactivation in the anterior cingulate cortex (ACC) and the amygdala in response to heat stimuli individually adjusted for equal subjective painfulness.¹¹ Beyond pain processing, patients with BPD have shown altered metabolic activity of prefrontal and limbic brain regions during rest and in the contexts of emotion regulation and inhibitory control.¹³⁻¹⁵ Taken together, painful stimulation may play an important role in self-regulatory mechanisms in BPD, e.g. in the context of self-injury.⁷

The so-called default mode network (DMN) has recently been studied in the contexts of both self-referential and pain processing.¹⁶⁻¹⁹ The DMN comprises the medial prefrontal cortex (mPFC), posterior cingulate/retrosplenial cortex (PCC/RSC) including the precuneus (PrC), inferior parietal lobule, lateral temporal cortex, and hippocampal formation.²⁰⁻²² Activity within the DMN has been observed when individuals are at rest or engaged in stimulus-unrelated thought – presumably facilitating a state of readiness to respond to environmental changes.^{20,23,24,25} Accumulating evidence suggests that the DMN comprises at least two interacting subsystems, the mPFC network and the PCC network, that serve specific, dissociable functions and may differentially modulate activity in so-called task-positive networks.²⁶⁻²⁹

Here, we were particularly interested in the interactions between the core nodes of the DMN, the PCC and the mPFC, with other brain regions during the perception of pain.^{30,31} Findings in healthy subjects indicate that painful stimulation leads to BOLD signal decreases and changes in brain regions known to be part of the functional architecture of the DMN.^{19,32-34} Painful electrical stimulation, for example, led to a significant recruitment of areas associated with cognitive and affective pain modulation, such as the ACC and middle frontal gyrus, into the DMN.^{19,35} However, the relationship between DMN connectivity and pain requires further investigation, especially regarding conditions of altered pain perception as observed in BPD. Therefore, the aforementioned lines of research are brought together.

While the DMN itself may not necessarily play a central role in pain processing in healthy subjects, probing its dynamic interactions and integrated performance with other brain regions may broaden our understanding of the neural substrates underlying reduced pain perception in BPD.^{38,39} To date, there is only one study³⁶ that has explicitly investigated DMN connectivity in BPD. In this study, BPD patients showed increased DMN connectivity during rest with the left DLPFC and the left insula as well as decreased connectivity with the left cuneus compared to HC. In the present study, we re-analyzed our previously published data,¹² using independent component analysis (ICA) and psychophysiological interaction (PPI) analysis, to investigate changes in DMN connectivity associated with the transition from a neutral temperature (considered to be a baseline condition for the present study) to painful thermal stimulation in BPD patients and HC.

Considering that BPD patients have previously demonstrated altered DMN connectivity with the DLPFC, cuneus and insula during rest,³⁶ as well as abnormal recruitment of prefrontal and limbic brain regions, such as the ACC and amygdala, in the contexts of emotion^{14,15} and pain processing,¹¹ we hypothesized that these brain regions would be differentially connected with the DMN in BPD patients. Consistent with previous findings,^{19,32} we also hypothesized that both groups would exhibit pain-related changes in connectivity with the two DMN nodes, particularly revealing a BOLD signal decrease and an increased recruitment of areas belonging to the “pain network”.^{30,31}

Methods

Participants

Twenty-five women with BPD, 92 percent of whom had a history of SIB, and 22 healthy age-matched women were included in our study. We have previously reported on this group of subjects in a study examining the neural correlates of antinociception in BPD.¹² Axis I and II diagnoses were assessed by a trained psychologist using the *Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)*³⁷ and the International Personality Disorder Examination (IPDE).³⁸ Trait dissociation was assessed in both groups with the German adaptation of the Dissociative Experience Scale (FDS).³⁹ The Dissociative States Scale (DSS)⁴⁰ was used to measure state dissociation and aversive inner tension immediately before and after scanning. BPD symptom severity was assessed with the Borderline Symptom List (BSL)^{41,42} and the number of DSM-IV criteria. Demographic and psychometric data are shown in Table 1.

All participants were right-handed and free of psychotropic and pain medications for at least two weeks prior to scanning. Exclusion criteria comprised a history of head trauma, chronic pain, serious medical or neurological illness, current major depression, alcohol or substance abuse or dependence in the last six months, lifetime bipolar disorder, schizophrenia, and pain disorders. Controls were excluded if they had a lifetime diagnosis of BPD as assessed by the *IPDE* or a current axis I diagnosis as assessed by the *SCID-I*.

Subjects provided written informed consent for the experimental procedures, which were approved by the ethics committee of the University of Heidelberg, Germany.

Stimulus Material and Procedure

All participants underwent psychophysical assessment and functional magnetic resonance imaging (fMRI) during heat stimulation versus neutral temperature in a block design. Heat stimuli were applied to the back of the right hand using the thermal sensory analyzer (TSA-II; Medoc Advanced Medical Systems, Ramat Yishai, Israel).

Psychophysical Assessment—We used the same methods described in detail in our previous studies to characterize pain sensitivity.^{11,12} Here, we focused on the stimulation with a temperature individually adjusted to a subjective pain intensity rating of 40 on a numeric rating scale (NRS) from 0 (no pain at all) to 100 (worst imaginable pain).

Functional Imaging—The second part of the experiment was performed on a 1.5-T magnetic resonance scanner equipped with a Vision gradient system and a circularly polarized head coil (Siemens Medical Solution, Erlangen, Germany). Scanning parameters and preprocessing procedures were previously described.^{11,12} As reported, five stimulation blocks with the individually adjusted temperature were applied. Each block lasted 30 seconds and was followed by 60-second intervals of neutral temperature (35°C, baseline). After each stimulation block, subjects rated their average pain intensity for that block using the NRS. To account for the change in temperature between neutral and pain blocks (rising and falling rates: 2°C per second), we removed the volumes “in between” and concatenated the ones that were acquired during stimulation with the target temperatures.

Image Analysis

Independent Component Analysis (ICA)—Group spatial ICA was conducted for all 47 subjects using the infomax algorithm⁴³ within the GIFT software (<http://icatb.sourceforge.net/>, version 1.3h). A detailed review of group ICA fMRI analyses can be found in Calhoun et al.^{44,45} In this study, the optimal number of independent components was found to be 29 using modified minimum description length criteria.⁴⁶ We launched the ICASSO algorithm,⁴⁷ implemented in GIFT, to increase the robustness of our independent components to initial algorithm conditions by repeating the ICA estimation 20 times. Single subject spatial maps and corresponding time courses were then computed (back-reconstructed) and converted to z-scores for display and use in subsequent statistical analyses. Each voxel in the brain has a z-score representing the strength of its contribution to the component’s time course.^{48,49}

Component Identification: The components related to the DMN were selected following visual inspection and methods previously described.⁵⁰⁻⁵² Details on the selection steps can be found in the supplementary online material.

Statistical Comparison of Images: For the selected components, the individual subject maps were entered into second-level analyses in SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/>), according to previous publications.^{52,53} For details, see the supplementary online material. Given the novelty of our approach and the lack of previous studies examining DMN connectivity during pain in BPD, the results of these analyses are reported at a statistical height threshold of $p < 0.005$ (uncorrected) at the voxel-level. Additionally, to correct for multiple comparisons across the whole brain, we used a cluster extent correction procedure to compute the number of expected voxels per cluster according to random field theory.⁵⁴ Thus, only clusters exceeding the respective number of voxels are presented.^{59-60,61} To control for differences in subjective pain intensity during the fMRI acquisition, we entered each subject’s average rating for the five “pain” blocks as a covariate of no interest into the two-sample t-tests comparing the component images of BPD patients and HC.

Statistical Comparison of Time Courses: Following methods previously described,^{45,55,56} multiple regression analysis, using the temporal sorting function in GIFT, was performed on the ICA time courses with the SPM8 design matrix. Details can be found in the supplementary online material. This procedure resulted in a set of beta-weights that were

entered into second-level analyses in SPSS for Windows (Rel. 18.0.0. 2009. Chicago: SPSS Inc.) to draw inferences about the degree of task-relatedness ($p < 0.05$).^{55,57, 62}

Correlation of Time Courses with symptom severity: Using Pearson correlation analysis, we also determined the relationship between DMN component time courses and patients' average BSL, DSS and FDS scores ($p < 0.05$, Bonferroni-corrected).

Psychophysiological Interaction (PPI) Analysis—Psychophysiological interaction (PPI) analysis is a hypothesis-driven approach to study context-specific changes in effective connectivity between one or more *a priori* defined brain regions of interest and the rest of the brain.⁵⁸ This is achieved by comparing connectivity in one context (in this case, “pain”) with connectivity in another context (here, “neutral”).

Using the PPI analysis methodology implemented in SPM8, we examined whether the PCC and mPFC²⁶ were differentially connected to other brain regions with respect to each other and to the experimental context of painful versus non-painful stimulation. For each subject, an average BOLD signal time course was extracted from the two seed regions, defined as a 10-mm sphere around coordinates derived from previous studies of the DMN.^{27,59} The PCC analysis was centered at Montreal Neurological Institute (MNI) coordinates 0, -57, 30 and the mPFC analysis at 0, 51, 0. Each PPI analysis was conducted individually for each subject and the two seed regions, focusing on two complementary contrasts, namely “neutral” greater “pain” and “pain” greater “neutral”.

Group Comparison: The resulting contrast images were entered into second-level within- and between-group analyses, using one- and two-sample t-tests, respectively. PPI results are reported at a statistical height threshold of $p < 0.005$ (uncorrected) at the voxel-level, in addition to the cluster-extent correction described above.⁵⁴ We additionally performed region-of-interest analyses for those brain regions that had previously shown altered connectivity with the DMN in patients with BPD, namely the DLPFC, insula and cuneus.³⁶ To identify whether these regions, showed a different pain-related coupling with the two seed regions in BPD patients compared to HC, we applied a more liberal height threshold of $p < 0.01$ (uncorrected). Correction for multiple comparisons was carried out using a small volume correction for these ROIs ($p < 0.05$, SVC-corrected).^{60,67} To control for differences in subjective pain intensity, we entered each subject's average rating for the five “pain” blocks as a covariate of no interest into the two-sample t-tests for “pain” greater “neutral”.

Results

Psychophysics

The two groups differed significantly in overall pain ratings when stimulated with different temperatures from 40°C to 48°C [analysis of variance for repeated measurements, main effect group: $F(1, 45) = 10.05$, $p = 0.003$]. The mean $\pm$ standard deviation (SD) individual temperatures derived from the psychophysical evaluation were significantly different between patients (45.86°C $\pm$ 1.31°C) and controls (44.60°C $\pm$ 1.22°C) [$t(45) = -3.40$, $p = .001$]. During fMRI, the two groups also differed significantly in their mean $\pm$ SD pain

intensity ratings for the individually adjusted temperature [patients: 47.3 ± 13.78 , controls: 63.93 ± 19.0 ; $t(45) = 3.464$, $p = 0.001$].

Independent Component Analysis

Component Identification—The selection process revealed three components that closely resembled our DMN mask and included brain areas previously implicated in the network²⁰: Component 28 ($r = 0.55$), component 13 ($r = 0.43$), and component 27 ($r = 0.29$) (Figure 1 and eTable 1). Component 28 included mainly the PCC/RSC/PrC, lateral parietal areas and superior/middle temporal gyri, but also smaller clusters within the mPFC, superior/middle frontal gyrus, insula and cerebellum (“posterior DMN”). Contributions of posterior DMN regions were also dominant in component 13, which included the PrC and a large cluster extending from the PCC along the cingulate gyrus. Component 27 received its strongest contributions from the mPFC and surrounding frontal areas (“anterior DMN”). The PCC/RSC/PrC and lateral parietal regions were also present, but to a lesser degree than in the other two components. Visual inspection confirmed that the same brain regions were included in the three selected components in both groups (eTable 2 and eTable 3).

Statistical Comparison of Images—Despite these similarities, two-sample t-tests yielded significant group differences in the integration of the left retrosplenial cortex (RSC) [$-12, -39, 3$; $t(44) = 4.16$] into component 28 and of the right inferior temporal gyrus (ITG) [$60, -9, -33$; $t(44) = 3.79$] and left superior frontal gyrus (SFG) [$-21, 30, 51$; $t(44) = 3.40$] into component 27. For those brain regions, patients showed less integration, i.e. decreased connectivity strength with other DMN areas,⁵² than HC (Figure 2). We did not find significant group differences in the connectivity of component 13.

Statistical Comparison of Time Courses—Temporal correlation analysis revealed that only components 28 and 27 showed significant signal decreases for “pain” relative to “neutral” in both groups. Component 13 was excluded from further analyses, since it failed to show significant signal change in response to “pain”. For the remaining DMN components, we did not find significant between-group differences in task-relatedness. However, among BPD patients, the degree of pain-related connectivity change of component 28 was positively correlated with subjects’ average BSL ($r = 0.63$) and FDS scores ($r = 0.59$). This indicates that worse symptom severity and higher trait dissociation are associated with less signal decrease of the “posterior DMN” in response to painful thermal stimulation. Since both measures were correlated with each other ($r = 0.52$, $p = 0.008$), only the correlation between BSL and relative signal decrease of component 28 is shown in Figure 3.

Psychophysiological Interaction Analysis

Within-group Analyses—Using PPI analyses, we found significant within-group differences in the connectivity maps of the two seed regions: While mPFC and PCC connectivity with a set of regions implicated in the DMN was stronger during “neutral” than “pain” (eTable 4), the two seed regions showed greater connectivity with only a few brain regions during “pain” than “neutral” (eTable 5). During “neutral” greater “pain”, the mPFC was significantly more correlated in both groups with adjacent voxels in the mPFC, bilateral

PCC/PrC, and superior/middle frontal gyrus. In controls, the mPFC was also more connected to the right fusiform/parahippocampal gyrus during “neutral” than “pain”. Regarding the PCC, controls showed greater connectivity during “neutral” than “pain” with adjacent voxels in the PCC/PrC, bilateral mPFC, left cerebellum, and bilateral fusiform/parahippocampal gyrus. Among patients, enhanced connectivity of this seed region during “neutral” greater “pain” was observed with bilateral superior temporal/angular gyri and adjacent voxels in the PCC. For “pain” greater “neutral”, only the patient group revealed enhanced connectivity of the PCC mPFC with the right inferior parietal lobule. In controls, we found greater correlation of the PCC during “pain” than “neutral” with left inferior frontal/superior temporal gyrus including the insula. Similarly, among patients, greater connectivity of the PCC during “pain” greater “neutral” was observed with bilateral inferior frontal/superior temporal gyri including the insula, bilateral inferior parietal lobule, left cerebellum, and left ACC.

Between-group Analyses—No brain areas showed significant between-group differences in connectivity with the mPFC for “pain” greater “neutral”. For “neutral” greater “pain”, controls showed significantly stronger mPFC connectivity with the left putamen (Figure 4). For the PCC, no brain areas exhibited significant between-group differences in connectivity for “neutral” greater “pain”. For “pain” greater “neutral”, controls showed significantly stronger PCC connectivity than the BPD group with the left DLPFC [−24, 54, 18; $t(43) = 3.40$; SVC-corrected³⁶] (Figure 4).⁴⁰

Discussion

To our knowledge, this is the first study to explore DMN connectivity during pain processing in patients with BPD, linking the previously separate research areas of DMN connectivity and altered pain perception in BPD. When compared to HC, patients with BPD showed significant alterations in DMN connectivity as determined by both ICA and PPI. Although the two methods are distinct in terms of methodology,²¹ we observed considerable overlap between the functional networks represented by components 27 and 28 and the PPI within-group results for “neutral” greater “pain”. Here, both methods clearly depict the functional architecture of DMN subnetworks.²¹ With regard to pain-related connectivity changes, ICA and PPI revealed different, but complementary aspects of DMN dysfunction and under-connectivity in BPD patients. Given that both methods revealed alterations involving the RSC/PCC, it may even be possible that the different aspects influence each other via this central node.

Independent Component Analysis

Using ICA, we first identified three components that closely resembled our mask and included brain areas previously associated with the DMN.²⁰ This differentiation supports the hypothesis that the DMN is more heterogeneous than widely assumed, and is in line with previous ICA studies that have identified separate DMN subnetworks with partially overlapping regions but distinctive time courses and connectivity patterns.^{26,52,61}

An examination of the component spatial maps revealed reduced connectivity of the left RSC, right ITG and left SFG with other DMN regions in patients compared to controls. The

RSC and neighboring PCC have previously been implicated in assessing the (emotional) salience and self-relevance of experimental stimuli,⁶²⁻⁶⁵ while the ITG has been linked to visual processing, multisensory integration and dissociative pathology.⁶⁶⁻⁶⁸ Although the SFG is not commonly associated with the DMN, a recent study has shown increased coupling of this region with the dorsal and ventral mPFC during self-relevant processing.²⁸ Due to its connections with the thalamus and the medial temporal lobe memory system, the RSC/PCC have been considered a critical hub for the integration of responses and the “switching” between different modes of processing.^{20,69,70} Taken together, we speculate that abnormal RSC/PCC connectivity may be related to difficulties of BPD patients to perceive painful stimuli as self-relevant and consequently switch from a baseline state of brain function to task-related states of information processing.

Our analysis of ICA time courses further indicates that this switching might be compromised in BPD, and that the extent of the deficiency reflects clinical measures of BPD. Specifically, the higher a patient scored on measures of symptom severity and trait dissociation, the less signal decrease was observed in her “posterior DMN” in response to “pain”. As recently discussed by Congdon et al.,⁷¹ attenuated DMN signal decrease during task performance may underlie impaired attentional and inhibitory control, and may therefore interfere with task-specific attention and goal-directed action.^{23,71} Since the analysis of beta-weights pertains to the component as a whole, we cannot infer that the difference in connectivity strength with the RSC is responsible for the attenuated signal decrease. However, in light of studies implicating the RSC in consciousness and reflective self-awareness,⁷²⁻⁷⁶ as well as in the switching between conditions,^{69,70} it would be plausible for the two observations to be connected.

Psychophysiological Interaction Analysis

Within-group Analyses—In accordance with previous reports of DMN heterogeneity, our PPI analyses revealed significant within-group differences in the connectivity maps of the PCC and mPFC.²⁶ In both groups, the two seed regions showed enhanced connectivity with other DMN regions during “neutral” greater “pain”, replicating findings by Bluhm et al.⁷⁷ In contrast, for “pain” greater “neutral”, only the BPD group showed enhanced mPFC connectivity with the right inferior parietal lobule. Regarding the PCC, both groups displayed increased connectivity for “pain” greater “neutral” with brain areas implicated in sensory integration and pain processing.^{30,78,79} The latter further supports the idea that the PCC functions as a “convergence node” within the DMN – or the brain in general, where information integration and the interaction between different subsystems are facilitated.^{20,62,63}

Between-group Analyses—Despite the abovementioned within-group differences, no brain areas showed significant between-group differences in connectivity with the mPFC for “pain” greater “neutral”. For “neutral” greater “pain”, controls showed significantly stronger mPFC connectivity with the left putamen. As part of the basal ganglia, the putamen has been implicated in motor control and various types of learning, e.g. reinforcement learning.⁸⁰⁻⁸² Our finding of enhanced mPFC connectivity with this region during “neutral” greater “pain” in controls versus patients may reflect underlying differences in the ability to regulate/inhibit

motor responses. Regarding the PCC, no brain areas exhibited significant between-group differences in connectivity for “neutral” greater “pain”. However, during “pain” greater “neutral”, controls showed significantly stronger PCC connectivity than patients with the left DLPFC. Activity in the DLPFC has been linked to response selection/inhibition, executive function, and cognitive control in the realms of emotion regulation, pain processing⁸³ and (working) memory⁸⁴⁻⁸⁶ – all of which are affected in BPD.^{11,14,87,88} In a study by Koenigsberg et al.,¹⁵ both BPD patients and HC showed joint recruitment of the DLPFC and PCC/PrC (among other regions) when attempting to downregulate negative emotions via psychological distancing. However, BPD patients engaged these cognitive control regions to a lesser extent than controls did,¹⁵ which is in line with our current findings.

The notion that the PCC interacts with the DLPFC to regulate emotions is also supported by Kraus et al. who reported a significant BOLD signal increase in the DLPFC and PCC in BPD patients, while they were imagining the emotional and cognitive reactions to a stressful situation.⁸⁹ Hence, we speculate that the significant between-group difference in PCC connectivity with the DLPFC for “pain” greater “neutral” may reflect altered cognitive modulation of the painful stimuli. This, in turn, may be due to (1) a diminished capacity for emotion regulation, leading to such severe behavioral consequences as SIB and dissociation, and/or (2) a different appraisal of the painful stimuli as less self-relevant and aversive. The former interpretation receives support from extant data linking frontolimbic dysfunction to emotional instability in BPD.^{14,88} The latter, on the other hand, is in line with the role of the DMN in self-related processing and the idea that pain may be associated with reward/negative reinforcement among BPD patients who self-injure to end states of aversive inner tension and dissociation.^{6,89} Taken together, we speculate that, although both groups experience the sensory component of pain and give pain ratings, their subjective experience may be qualitatively different. In other words, painful stimulation may have a different impact on the self-monitoring system of BPD patients: Whereas controls are more likely to experience pain as an aversive threat that has to be avoided or down-regulated (thus engaging the DLPFC), pain may actually be perceived as soothing by patients with BPD.^{6,7} However, these interpretations should be considered speculative since we did not include a detailed assessment of the subjective unpleasantness and self-relevance of the stimuli.

Limitations

There are several limitations of the present study.

First, because the majority of patients had a history of SIB, it cannot be determined whether our findings are related to SIB *per se* or BPD psychopathology in general. Longitudinal studies comparing BPD patients with SIB to BPD patients who never self-injured are needed to resolve this issue.

It should also be noted that controls and patients differed significantly in their average intensity ratings for the “pain” blocks during the fMRI acquisition as compared to the psychophysiological assessment prior to the fMRI scan. The individual adjustment of temperatures was conducted immediately before fMRI scanning. During scanning, individual ratings were repeated and may differ from pre-scanning ratings, as was the case

here for HC. To control for these differences in subjective pain intensity, we entered each subject's average pain rating for the individually-adjusted temperature as a covariate into the PPI between-group comparisons for "pain" greater "neutral". Given that the actual temperature stimuli were higher for BPD patients, it may also be possible that the observed group differences represent differences in stimulus intensity rather than basic group differences in connectivity. However, this explanation is unlikely because responses in prefrontal and parietal brain regions have been related to stimulus perception and subsequent cognitive processing irrespective of perceived pain or stimulus intensity.^{33,90} Thus, we decided to control only for the differences in subjective pain intensity.

Moreover, since alterations in DMN connectivity and/or pain processing have also been reported in other psychiatric disorders,⁹¹ such as depression,^{92,93} PTSD related to early life trauma,⁹⁴ and social anxiety disorder,⁹⁵ the interpretation of our findings may be limited by the presence of such comorbidities in our patient sample. Thus, future studies should include other clinical control groups to clarify whether our findings are specific to BPD.

Although ICA and PPI analyses are well-established and provide useful complements to traditional GLM subtraction analyses, it is important to acknowledge different sources of investigator-specific bias and thus variability in their outcomes.^{21,96} Potential biases result from the *a priori* selection of seed regions in PPI and the use of different model orders and spatial templates in ICA. Similarly, although DMN connectivity during pain, rather than pain processing *per se*, was the main focus of the current study, our PPI results are limited by modeling the connections of only two seed regions. It is possible, for example, that the interaction between the PCC and DLPFC could be mediated through a third area, or that a third area may provide common input to both.⁵⁸ According to Friston et al.,⁵⁸ this common input would itself be context-sensitive and could be identified using PPI analysis with the third area as the seed region. Hence, given the pivotal role of the anterior and midcingulate cortices in pain processing and their connections with both the PCC and prefrontal cortex,^{34,64} future studies should place additional seeds in those cingulate regions.

Finally, further research is necessary to determine whether the observed alterations in DMN connectivity in BPD are limited to painful thermal stimulation or if they generalize to other tasks, such as the processing of social and autobiographical stimuli, for example.⁹⁷ Since BPD patients tend to over-interpret neutral or ambiguous stimuli as self-referential,^{92,103} one could test the hypothesis that group differences in DMN connectivity are, in fact, mediated by a different appraisal of the stimuli as (more or less) self-relevant and aversive.

Conclusion

In summary, the present evidence suggests that patients with BPD show significant alterations in DMN connectivity with differences in spatial integrity and temporal characteristics. These alterations may reflect a different cognitive and affective appraisal of pain as less self-relevant and aversive, and a deficiency in the switching between baseline and task-related processing. This deficiency may, in turn, be related to everyday difficulties of BPD patients to regulate their emotions, focus mindfully on one task at a time, and efficiently shift their attention from one task to another.^{98,99} Hence, the present results may be incorporated into the advancement of mindfulness-based treatments, such as dialectical

behavior therapy,^{100,101} to help BPD patients engage in an activity with full alertness and awareness of themselves and their bodily sensations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

The upper section depicts a composite view of the 3 ICA components representing the default mode subnetworks. These spatial maps and time courses were identified by GIFT and correspond to the mean component estimates of all 47 subjects (BPD patients and HC). The lower section shows the statistical parametric maps of these components created in SPM8. From left to right: component 28, component 27, and component 13.

Figure 2.

Group differences in the default mode sub-networks. Compared to healthy controls, BPD patients showed significantly less integration of the left RSC $[-12, -39, 3; t(44) = 4.16]$ (left) into component 28 and of the right ITG $[60, -9, -33; t(44) = 3.79]$ (middle) and left SFG $[-21, 30, 51; t(44) = 3.40]$ (right) into component 27. Each map is masked with the corresponding mask generated from all subjects (see Fig. 1) and thresholded at $p < 0.005$, (uncorrected) in an addition to a cluster-extent threshold based on random field theory.⁵⁴

Figure 3.

The graph shows the negative correlation between the relative connectivity change of component 28 from “neutral” to “pain” and BSL scores in patients with BPD ($p < 0.05$, Bonferroni-corrected).

Figure 4.

Group difference in mPFC seed region connectivity. During “neutral” greater “pain”, patients with BPD showed significantly less connectivity of the mPFC seed region with the left putamen $[-18, -15, -12; t(44) = 3.30]$. This cluster is significant at $p < 0.005$, (uncorrected) at the voxel level in an addition to a cluster-extent threshold based on random field theory.⁵⁴

Figure 5.

Group difference in PCC seed region connectivity. During “pain” greater “neutral”, patients with BPD showed significantly less connectivity of the PCC seed region with the left DLPFC [$-24, 54, 18$; $t(43) = 3.40$; $p < .05$, SVC-corrected].

Table 1
Demographic and Psychometric Data

	Patients with BPD (n = 25)	Controls (n = 22)
Age, mean $\pm$ SD, y	28.48 $\pm$ 7.12	28.23 $\pm$ 8.37 [*]
BSL score, mean $\pm$ SD	1.76 $\pm$ 0.66	
No. of DSM-IV BPD criteria fulfilled	6.54 $\pm$ 1.22	
FDS score, mean $\pm$ SD	20.81 $\pm$ 10.17	3.38 $\pm$ 2.58 [†]
DSS score, mean $\pm$ SD	0.65 $\pm$ 0.82	0.13 $\pm$ 0.32 [*]
Aversive inner tension	3.44 $\pm$ 2.14	1.00 $\pm$ 1.38 [†]
Current SIB ([past] No.)	17 [6]	
Axis I comorbidity (current [past] No.)	Major depressive disorder (0 [18])	None
	Dysthymia (2)	
	Panic disorder without agoraphobia (7)	
	Panic disorder with agoraphobia (2 [1])	
	Agoraphobia without panic disorder (1)	
	Posttraumatic stress disorder (9)	
	Social phobia (10)	
	General anxiety disorder (3)	
	Specific phobia (1)	
	Obsessive-compulsive disorder (3 [1])	
	Anorexia nervosa (0 [2])	
	Bulimia nervosa (2 [4])	
	Binge eating disorder (2)	
	Alcohol abuse (0 [2])	
	Cannabinoid abuse (0 [1])	
	Cocaine dependence (0 [3])	
	Sedative dependence (0 [1])	
	Polydrug dependence (0 [1])	
Axis II comorbidity (No.)	Avoidant PD (5)	None
	Histrionic PD (1)	
	Narcissistic PD (1)	
	Dependent PD (1)	

Abbreviations: BPD = Borderline personality disorder; BSL = Borderline Symptom List; DSS = Dissociative States Scale (state dissociation); FDS = Fragebogen zur Erfassung Dissoziativer Symptome (German adaptation of the Dissociative Experience Scale) (trait dissociation); PD = personality disorder.

^{*} Not statistically significant.

[†] $p < 0.05$ using a 2-tailed t-test.