

# Alterations in Default Mode Network Connectivity During Pain Processing in Borderline Personality Disorder

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**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 signal decreases and changes in the functional architecture of the DMN.

**Objectives:** To connect the previously separate research areas of DMN connectivity and altered pain perception in BPD and to explore DMN connectivity during pain processing in patients with BPD.

**Design:** Case-control study.

**Setting:** University hospital.

**Participants:** Twenty-five women with BPD, including 23 (92%) with a history of self-harm, and 22 age-matched control subjects.

**Interventions:** Psychophysical assessment and functional magnetic resonance imaging during painful heat vs neutral temperature stimulation.

**Main Outcome Measure:** Connectivity of DMN as assessed via independent component analysis and psychophysiological interaction analysis.

**Results:** Compared with control subjects, 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 vs neutral, patients with BPD exhibited less posterior cingulate cortex seed region connectivity with the left dorsolateral prefrontal cortex.

**Conclusions:** 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 as well as a deficiency in the switching between baseline and task-related processing. This deficiency may be related to everyday difficulties of patients with BPD in regulating their emotions, focusing mindfully on 1 task at a time, and efficiently shifting their attention from one task to another.

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**P**ATIENTS WITH BORDERLINE personality disorder (BPD) frequently experience stress-induced aversive states of inner tension and dissociation,<sup>1,2</sup> which are often associated with analgesia and self-injurious behavior (SIB).<sup>3,4</sup> Specifically, many patients with BPD engage in SIB to regulate affect, decrease dissociation, and regain awareness of physical sensations.<sup>5-7</sup> 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.<sup>8-10</sup> Instead, findings from pain

research using a thermal stimulation paradigm suggest that patients with BPD show altered activity in brain regions implicated in the cognitive and affective evaluation of pain.<sup>11,12</sup> Compared with healthy control subjects, patients with BPD displayed increased activation in the dorsolateral prefrontal cortex (DLPFC) coupled with deactivation in the anterior cingulate cortex and the amygdala in response to heat stimuli individually adjusted for equal subjective painfulness.<sup>11</sup> 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 inhibi-

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**Table. Demographic and Psychometric Data**

Characteristic	Patients With BPD (n = 25)	Control Subjects (n = 22)
Age, mean (SD), y	28.48 (7.12)	28.23 (8.37) <sup>a</sup>
BSL score, mean (SD)	1.76 (0.66)	...
DSM-IV BPD criteria fulfilled, mean (SD), No.	6.54 (1.22)	...
FDS score, mean (SD)	20.81 (10.17)	3.38 (2.58) <sup>b</sup>
DSS score, mean (SD)	0.65 (0.82)	0.13 (0.32) <sup>a</sup>
Aversive inner tension, mean (SD)	3.44 (2.14)	1.00 (1.38) <sup>b</sup>
SIB, current (past), No.	17 (6)	...
Axis I comorbidity, current (past), No.		
Major depressive disorder	0 (18)	...
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	...
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 zu Dissoziativen Symptomen (German adaptation of the Dissociative Experience Scale, trait dissociation); PD, personality disorder; SIB, self-injurious behavior; ellipses, not applicable.

<sup>a</sup>Not statistically significant ( $P > .05$ ).

<sup>b</sup> $P < .05$  using a 2-tailed  $t$  test.

tory control.<sup>13-15</sup> Taken together, painful stimulation may play an important role in self-regulatory mechanisms in BPD, eg, in the context of SIB.<sup>7</sup>

The so-called default mode network (DMN) has recently been studied in the contexts of both self-referential and pain processing.<sup>16-19</sup> The DMN comprises the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC)/retrosplenial cortex (RSC) including the precuneus (PrC), inferior parietal lobule, lateral temporal cortex, and hippocampal formation.<sup>20-22</sup> 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.<sup>20,23-25</sup> Accumulating evidence suggests that the DMN comprises at least 2 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.<sup>26-29</sup>

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 percep-

tion of pain.<sup>30,31</sup> Findings in healthy subjects indicate that painful stimulation leads to blood oxygenation level-dependent signal decreases and changes in brain regions known to be part of the functional architecture of the DMN.<sup>19,32-34</sup> Painful electrical stimulation, for example, led to a significant recruitment of areas associated with cognitive and affective pain modulation, such as the anterior cingulate cortex and middle frontal gyrus, into the DMN.<sup>19,35</sup> 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. To our knowledge, only 1 study<sup>36</sup> to date has explicitly investigated DMN connectivity in BPD. In this study, patients with BPD showed increased DMN connectivity during rest with the left DLPFC and the left insula as well as decreased connectivity with the left cuneus compared with healthy control subjects. In the present study, we reanalyzed our previously published data<sup>12</sup> 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 patients with BPD and healthy control subjects.

Considering that patients with BPD have previously demonstrated altered DMN connectivity with the DLPFC, cuneus, and insula during rest<sup>36</sup> as well as abnormal recruitment of prefrontal and limbic brain regions such as the anterior cingulate cortex and amygdala in the contexts of emotion<sup>14,15</sup> and pain processing,<sup>11</sup> we hypothesized that these brain regions would be differentially connected with the DMN in patients with BPD. Consistent with previous findings,<sup>19,32</sup> we also hypothesized that both groups would exhibit pain-related changes in connectivity with the 2 DMN nodes, particularly revealing a blood oxygenation level-dependent signal decrease and an increased recruitment of areas belonging to the pain network.<sup>30,31</sup>

## METHODS

### PARTICIPANTS

Twenty-five women with BPD, 23 (92%) of whom had a history of SIB, and 22 healthy age-matched women were included in our study. We have previously described this group of subjects in a study examining the neural correlates of antinociception in BPD.<sup>12</sup> Axis I and II diagnoses were assessed by a trained psychologist using the *Structured Clinical Interview for DSM-IV Axis I Disorders*<sup>37</sup> and the *International Personality Disorder Examination*.<sup>38</sup> Trait dissociation was assessed in both groups with the German adaptation of the Dissociative Experience Scale.<sup>39</sup> The Dissociative States Scale<sup>40</sup> was used to measure state dissociation and aversive inner tension immediately before and after scanning. The severity of BPD symptoms was assessed with the Borderline Symptom List<sup>41,42</sup> and the number of DSM-IV criteria. Demographic and psychometric data are shown in the **Table**.

All participants were right-handed and free of psychotropic and pain medications for at least 2 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 6 months, lifetime bipolar disorder, schizophrenia, and pain disorders. Control subjects were excluded if they had a lifetime diagnosis of BPD as assessed by the *International Personality Disorder Examination* or a current Axis I diagnosis as assessed by the *Structured Clinical Interview for DSM-IV Axis I Disorders*.

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

## STIMULUS MATERIAL AND PROCEDURE

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

### Psychophysical Assessment

We used the same methods described in detail in our previous studies to characterize pain sensitivity.<sup>11,12</sup> Here, we focused on the stimulation with a temperature individually adjusted to a subjective pain intensity rating of 40 on a numeric rating scale ranging 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 Solutions). Scanning parameters and preprocessing procedures were previously described.<sup>11,12</sup> As reported, 5 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 numeric rating scale. To account for the change in temperature between neutral and pain blocks (increasing and decreasing rates: 2°C per second), we removed the volumes between and concatenated those acquired during stimulation with the target temperatures.

## IMAGE ANALYSIS

### Independent Component Analysis

Group spatial ICA was conducted for all 47 subjects using the infomax algorithm<sup>43</sup> within GIFT version 1.3h software (<http://icatb.sourceforge.net/>). A detailed review of group ICA fMRI analyses can be found in the articles by Calhoun et al.<sup>44,45</sup> In this study, the optimal number of independent components was found to be 29 using modified minimum description length criteria.<sup>46</sup> We launched the ICASSO algorithm,<sup>47</sup> implemented in the GIFT software, 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.<sup>48,49</sup>

**Component Identification.** The components related to the DMN were selected following visual inspection and methods previously described.<sup>50-52</sup> Details on the selection steps can be found in the eAppendix (<http://www.archgenpsychiatry.com>).

**Statistical Comparison of Images.** For the selected components, the individual subject maps were entered into second-level analyses in SPM8 software (<http://www.fil.ion.ucl.ac.uk/spm/>) according to previous publications.<sup>32,53</sup> For details, see the eAppendix. 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  $P < .005$  (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.<sup>54</sup> Thus, only clusters exceeding the respective number of voxels are presented. To control for differences in subjective pain intensity during fMRI acquisition, we entered each subject's average rating for the 5 pain blocks as a covariate of no interest into the 2-sample *t* tests comparing the component images of patients with BPD and healthy control subjects.

**Statistical Comparison of Time Courses.** Following methods previously described,<sup>45,55,56</sup> multiple regression analysis using the temporal sorting function in the GIFT software was performed on the ICA time courses with the SPM8 design matrix. Details can be found in the eAppendix. This procedure resulted in a set of  $\beta$  weights that were entered into second-level analyses in SPSS version 18.0.0 for Windows (SPSS Inc) to draw inferences about the degree of task relatedness ( $P < .05$ ).<sup>55,57</sup>

**Correlation of Time Courses With Symptom Severity.** Using Pearson correlation analysis, we also determined the relationship between DMN component time courses and patients' average Borderline Symptom List, Dissociative States Scale, and Dissociative Experience Scale scores ( $P < .05$ , Bonferroni corrected).

### PPI Analysis

A PPI analysis is a hypothesis-driven approach to study context-specific changes in effective connectivity between 1 or more a priori-defined brain regions of interest and the rest of the brain.<sup>58</sup> This is achieved by comparing connectivity in one context (in this case, pain) with connectivity in another context (here, neutral).

Using the PPI analysis method implemented in SPM8 software, we examined whether the PCC and mPFC<sup>26</sup> were differentially connected to other brain regions with respect to each other and to the experimental context of painful vs nonpainful stimulation. For each subject, an average blood oxygenation level-dependent signal time course was extracted from the 2 seed regions, defined as a 10-mm sphere around coordinates derived from previous studies of the DMN.<sup>27,59</sup> The PCC analysis was centered at Montreal Neurological Institute (MNI) coordinates 0, -57, 30, and the mPFC analysis was centered at MNI coordinates 0, 51, 0. Each PPI analysis was conducted individually for each subject and the 2 seed regions, focusing on 2 complementary contrasts, namely neutral greater than pain and pain greater than neutral.

The resulting contrast images were entered into second-level within- and between-group analyses using 1- and 2-sample *t* tests, respectively. The PPI analysis results are reported at a statistical height threshold of  $P < .005$  (uncorrected) at the voxel level in addition to the cluster-extent correction described earlier.<sup>54</sup> 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.<sup>36</sup> To identify whether these regions showed a different pain-related coupling with the 2 seed regions in patients with BPD compared with healthy control subjects, we applied a more liberal height threshold of  $P < .01$  (uncorrected). Correction for multiple comparisons was carried out using a small-volume correction for these regions of interest ( $P < .05$ , small-volume corrected).<sup>60</sup> To control for differences in subjective pain intensity, we entered each subject's average rating for the 5 pain blocks as a covariate of no interest into the 2-sample  $t$  tests for pain greater than neutral.

## RESULTS

### PSYCHOPHYSICS

The 2 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:  $F_{1,45} = 10.05$ ;  $P = .003$ ). The mean (SD) individual temperatures derived from the psychophysical evaluation were significantly different between patients with BPD (45.86°C [1.31°C]) and healthy control subjects (44.60°C [1.22°C]) ( $t_{45} = -3.40$ ;  $P = .001$ ). During fMRI, patients with BPD differed significantly from healthy control subjects in their mean (SD) pain intensity ratings for the individually adjusted temperature (47.3 [13.78] vs 63.93 [19.0], respectively;  $t_{45} = 3.46$ ;  $P = .001$ ).

### INDEPENDENT COMPONENT ANALYSIS

#### Component Identification

The selection process revealed 3 components that closely resembled our DMN mask and included brain areas previously implicated in the network<sup>20</sup>: 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 included 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 2 components. Visual inspection confirmed that the same brain regions were included in the 3 selected components in both groups (eTable 2 and eTable 3).

#### Statistical Comparison of Images

Despite these similarities, 2-sample  $t$  tests yielded significant group differences in the integration of the left RSC (MNI coordinates -12, -39, 3;  $t_{44} = 4.16$ ) into component 28 and of the right inferior temporal gyrus (MNI coordinates 60, -9, -33;  $t_{44} = 3.79$ ) and left superior frontal gyrus (MNI coordinates -21, 30, 51;  $t_{44} = 3.40$ ) into component 27. For those brain regions, patients with BPD showed less integration, ie, decreased connectivity

strength with other DMN areas,<sup>52</sup> than healthy control subjects (**Figure 2**). We did not find significant group differences in the connectivity of component 13.

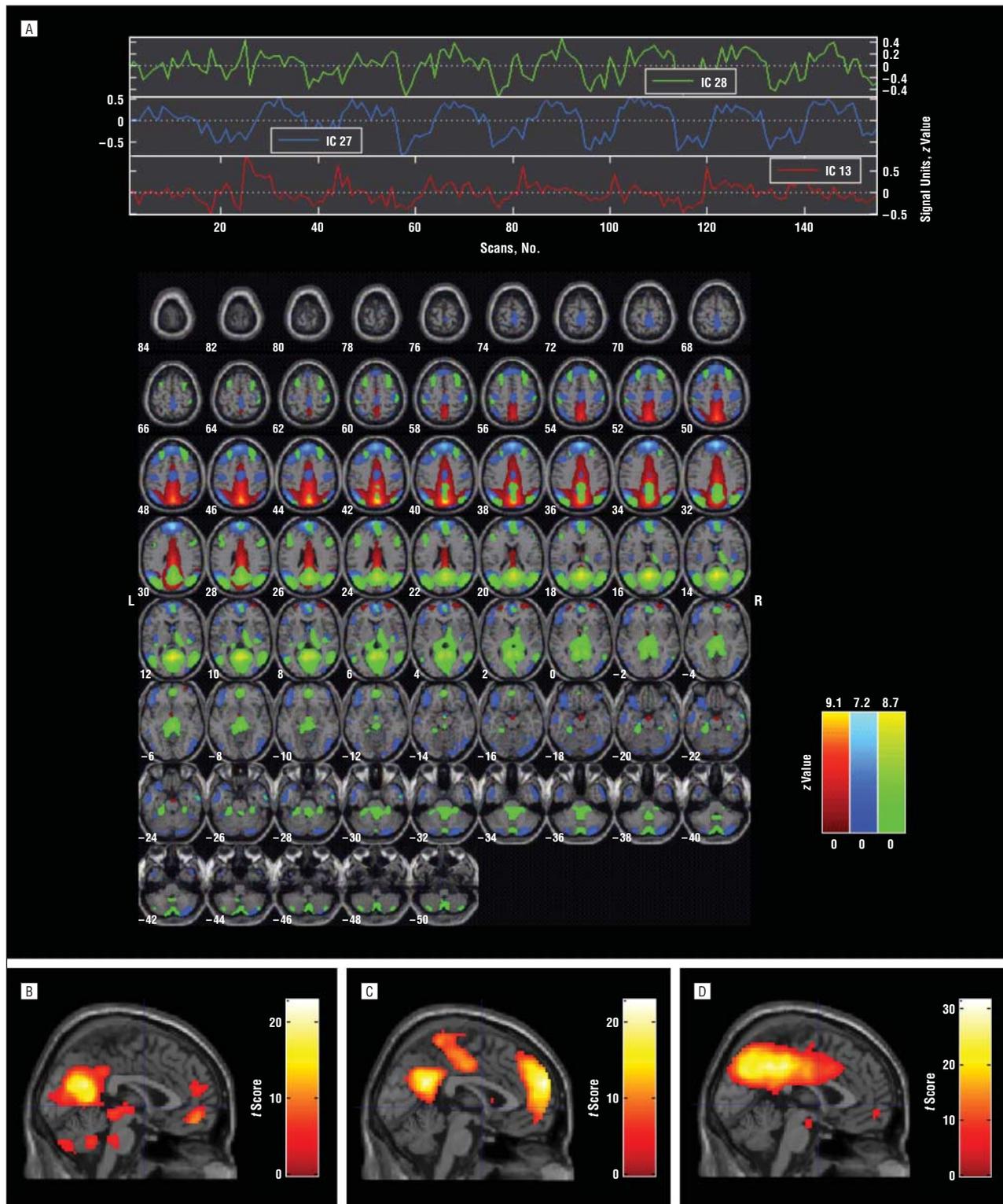
#### Statistical Comparison of Time Courses

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 because 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 patients with BPD, the degree of pain-related connectivity change of component 28 was positively correlated with subjects' average Borderline Symptom List ( $r = 0.63$ ) and Dissociative Experience Scale ( $r = 0.59$ ) scores. 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. Because both measures were correlated with each other ( $r = 0.52$ ;  $P = .008$ ), only the correlation between the Borderline Symptom List score and the relative signal decrease of component 28 is shown in **Figure 3**.

### PPI ANALYSIS

#### Within-Group Analyses

Using PPI analyses, we found significant within-group differences in the connectivity maps of the 2 seed regions: while mPFC and PCC connectivity with a set of regions implicated in the DMN was stronger during neutral than during pain (eTable 4), the 2 seed regions showed greater connectivity with only a few brain regions during pain than during neutral (eTable 5). During neutral greater than 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 control subjects, the mPFC was also more connected to the right fusiform/parahippocampal gyrus during neutral than during pain. Regarding the PCC, control subjects showed greater connectivity during neutral than during pain with adjacent voxels in the PCC/PrC, bilateral mPFC, left cerebellum, and bilateral fusiform/parahippocampal gyrus. Among patients with BPD, enhanced connectivity of this seed region during neutral greater than pain was observed with bilateral superior temporal/angular gyri and adjacent voxels in the PCC. For pain greater than neutral, only the patients with BPD revealed enhanced connectivity of the mPFC with the right inferior parietal lobule. In control subjects, we found greater correlation of the PCC during pain than during neutral with the left inferior frontal/superior temporal gyrus including the insula. Similarly, among patients with BPD, greater connectivity of the PCC during pain greater than neutral was observed with bilateral inferior frontal/superior temporal gyri including the insula, bilateral inferior parietal lobule, left cerebellum, and left anterior cingulate cortex.

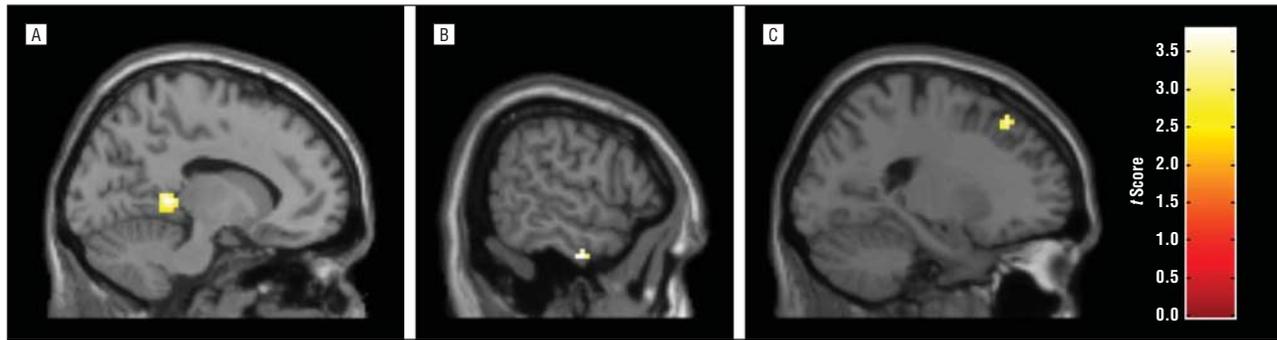


**Figure 1.** The 3 independent component analysis components representing the default mode subnetworks. A, Composite view of the 3 independent component analysis components. These spatial maps and time courses were identified by GIFT software and correspond to the mean component estimates of all 47 subjects (patients with borderline personality disorder and healthy control subjects). L indicates left; R, right. The statistical parametric maps of components 28 (B), 27 (C), and 13 (D) were created in SPM8 software.

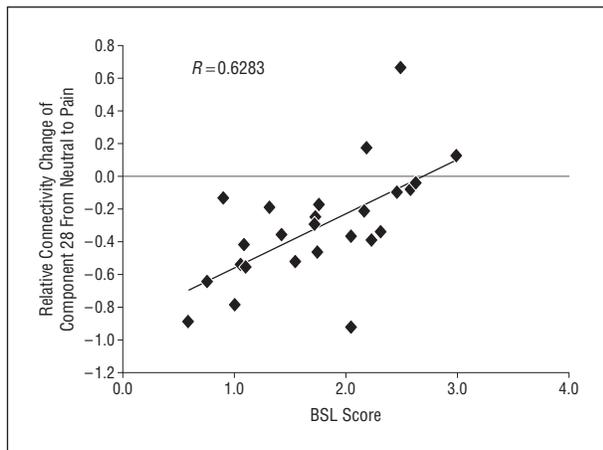
### Between-Group Analyses

No brain areas showed significant between-group differences in connectivity with the mPFC for pain greater than

neutral. For neutral greater than pain, control subjects showed significantly stronger mPFC connectivity with the left putamen (**Figure 4**). For the PCC, no brain areas exhibited significant between-group differences in con-



**Figure 2.** Group differences in the default mode subnetworks. Compared with healthy control subjects, patients with borderline personality disorder showed significantly less integration of the left retrosplenial cortex (Montreal Neurological Institute coordinates  $-12, -39, 3$ ;  $t_{44}=4.16$ ) (A) into component 28 and of the right inferior temporal gyrus (Montreal Neurological Institute coordinates  $60, -9, -33$ ;  $t_{44}=3.79$ ) (B) and left superior frontal gyrus (Montreal Neurological Institute coordinates  $-21, 30, 51$ ;  $t_{44}=3.40$ ) (C) into component 27. Each map is masked with the corresponding mask generated from all subjects (Figure 1) and thresholded at  $P < .005$ , (uncorrected) in addition to a cluster-extent threshold based on random field theory.<sup>54</sup>

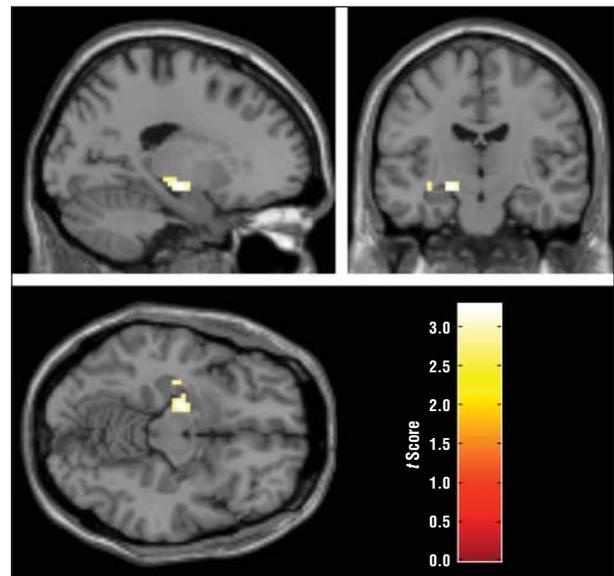


**Figure 3.** Negative correlation between the relative connectivity change of component 28 from neutral to pain and Borderline Symptom List (BSL) scores in patients with borderline personality disorder ( $P < .05$ , Bonferroni corrected).

nectivity for neutral greater than pain. For pain greater than neutral, control subjects showed significantly stronger PCC connectivity than the patients with BPD with the left DLPFC (MNI coordinates  $-24, 54, 18$ ;  $t_{43}=3.40$ , small-volume corrected<sup>36</sup>) (**Figure 5**).

#### COMMENT

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 with healthy control subjects, patients with BPD showed significant alterations in DMN connectivity as determined by both ICA and PPI analysis. Although the 2 methods are distinct in terms of methodology,<sup>21</sup> we observed considerable overlap between the functional networks represented by components 27 and 28 and the PPI analysis within-group results for neutral greater than pain. Here, both methods clearly depict the functional architecture of DMN subnetworks.<sup>21</sup> With regard to pain-related connectivity changes, ICA and PPI analysis revealed different but complementary aspects of DMN dysfunction and underconnectivity in patients with BPD.



**Figure 4.** Group difference in medial prefrontal cortex seed region connectivity. During neutral greater than pain, patients with borderline personality disorder showed significantly less connectivity of the medial prefrontal cortex seed region with the left putamen (Montreal Neurological Institute coordinates  $-18, -15, -12$ ;  $t_{44}=3.30$ ). This cluster is significant at  $P < .005$  (uncorrected) at the voxel level in addition to a cluster-extent threshold based on random field theory.<sup>54</sup>

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 3 components that closely resembled our mask and included brain areas previously associated with the DMN.<sup>20</sup> 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.<sup>26,52,61</sup>

An examination of the component spatial maps revealed reduced connectivity of the left RSC, right inferior temporal gyrus, and left superior frontal gyrus with other

DMN regions in patients with BPD compared with control subjects. The RSC and neighboring PCC have previously been implicated in assessing the (emotional) salience and self-relevance of experimental stimuli,<sup>62-65</sup> while the inferior temporal gyrus has been linked to visual processing, multisensory integration, and dissociative pathology.<sup>66-68</sup> Although the superior frontal gyrus 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.<sup>28</sup> Owing to its connections with the thalamus and the medial temporal lobe memory system, the RSC and PCC have been considered a critical hub for the integration of responses and the switching between different modes of processing.<sup>20,69,70</sup> Taken together, we speculate that abnormal RSC/PCC connectivity may be related to difficulties of patients with BPD in perceiving painful stimuli as self-relevant and consequently switching 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,<sup>71</sup> 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.<sup>23,71</sup> Because 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<sup>72-76</sup> as well as in the switching between conditions,<sup>69,70</sup> it would be plausible for the 2 observations to be connected.

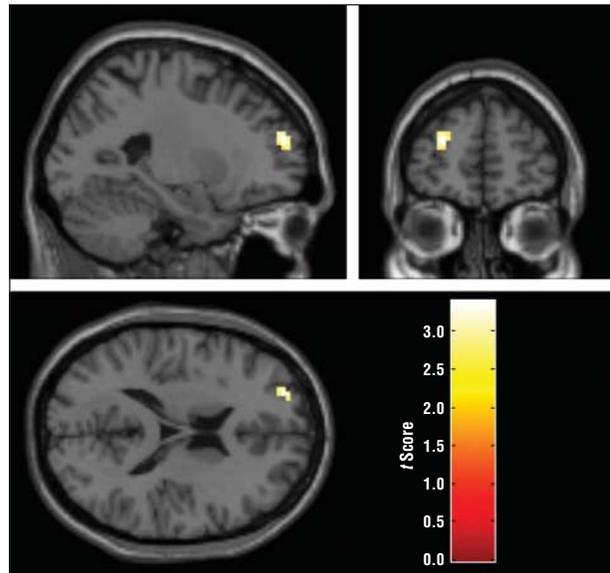
## PPI ANALYSIS

### 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.<sup>26</sup> In both groups, the 2 seed regions showed enhanced connectivity with other DMN regions during neutral greater than pain, replicating findings by Bluhm et al.<sup>77</sup> In contrast, for pain greater than neutral, only patients with BPD showed enhanced mPFC connectivity with the right inferior parietal lobule. Regarding the PCC, both groups displayed increased connectivity for pain greater than neutral with brain areas implicated in sensory integration and pain processing.<sup>30,78,79</sup> 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.<sup>20,62,63</sup>

### Between-Group Analyses

Despite the aforementioned within-group differences, no brain areas showed significant between-group differences



**Figure 5.** Group difference in posterior cingulate cortex seed region connectivity. During pain greater than neutral, patients with borderline personality disorder showed significantly less connectivity of the posterior cingulate cortex seed region with the left dorsolateral prefrontal cortex (Montreal Neurological Institute coordinates  $-24, 54, 18$ ;  $t_{43}=3.40$ ;  $P < .05$ , small-volume corrected).

in connectivity with the mPFC for pain greater than neutral. For neutral greater than pain, control subjects 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, eg, reinforcement learning.<sup>80-82</sup> Our finding of enhanced mPFC connectivity with this region during neutral greater than pain in control subjects vs patients with BPD may reflect underlying differences in the ability to regulate or inhibit motor responses. Regarding the PCC, no brain areas exhibited significant between-group differences in connectivity for neutral greater than pain. However, during pain greater than neutral, control subjects showed significantly stronger PCC connectivity than patients with BPD with the left DLPFC. Activity in the DLPFC has been linked to response selection or inhibition, executive function, and cognitive control in the realms of emotion regulation, pain processing,<sup>83</sup> and (working) memory<sup>84-86</sup>—all of which are affected in BPD.<sup>11,14,87,88</sup> In a study by Koenigsberg et al,<sup>15</sup> both patients with BPD and healthy control subjects showed joint recruitment of the DLPFC and PCC/PrC (among other regions) when attempting to downregulate negative emotions via psychological distancing. However, patients with BPD engaged these cognitive control regions to a lesser extent than control subjects did,<sup>15</sup> 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,<sup>89</sup> who reported a significant blood oxygenation level–dependent signal increase in the DLPFC and PCC in patients with BPD while they were imagining the emotional and cognitive reactions to a stressful situation. Hence, we speculate that the significant between-group difference in PCC connectivity with the DLPFC for pain greater than neutral may reflect altered cognitive modulation of the painful stimuli. This in turn may be due to (1) a diminished capacity for emo-

tion 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.<sup>14,88</sup> 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 negative reinforcement among patients with BPD who self-injure to end states of aversive inner tension and dissociation.<sup>6,89</sup> 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 effect on the self-monitoring system of patients with BPD: whereas control subjects are more likely to experience pain as an aversive threat that has to be avoided or downregulated (thus engaging the DLPFC), patients with BPD may actually perceive pain as soothing.<sup>6,7</sup> However, these interpretations should be considered speculative because we did not include a detailed assessment of the subjective unpleasantness and self-relevance of the stimuli.

### LIMITATIONS

There are several limitations of this study. First, because most 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 patients with both BPD and SIB with patients with BPD who never self-injured are needed to resolve this issue.

It should also be noted that control subjects and patients with BPD differed significantly in their average intensity ratings for the pain blocks during the fMRI acquisition as compared with 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 prescanning ratings, as was the case here for healthy control subjects. 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 than neutral. Given that the actual temperature stimuli were higher for patients with BPD, 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.<sup>33,90</sup> Thus, we decided to control only for the differences in subjective pain intensity.

Moreover, because alterations in DMN connectivity and/or pain processing have also been reported in other psychiatric disorders<sup>91</sup> such as depression,<sup>92,93</sup> posttraumatic stress disorder related to early life trauma,<sup>94</sup> and social anxiety disorder,<sup>95</sup> 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 analysis are well established and provide useful complements to traditional general linear model subtraction analyses, it is important to acknowledge different sources of investigator-specific bias and thus variability in their outcomes.<sup>21,96</sup> Potential biases result from the a priori selection of seed regions in PPI analysis 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 this study, our PPI analysis results are limited by modeling the connections of only 2 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.<sup>58</sup> According to Friston et al,<sup>58</sup> 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,<sup>34,64</sup> 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 whether they generalize to other tasks such as the processing of social and autobiographical stimuli.<sup>97</sup> Because patients with BPD tend to overinterpret neutral or ambiguous stimuli as self-referential,<sup>87,98</sup> 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.

### CONCLUSIONS

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 as well as a deficiency in the switching between baseline and task-related processing. This deficiency may in turn be related to everyday difficulties of patients with BPD in regulating their emotions, focusing mindfully on 1 task at a time, and efficiently shifting their attention from one task to another.<sup>98,99</sup> Hence, the present results may be incorporated into the advancement of mindfulness-based treatments such as dialectical behavior therapy<sup>100,101</sup> to help patients with BPD engage in an activity with full alertness and awareness of themselves and their bodily sensations.

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