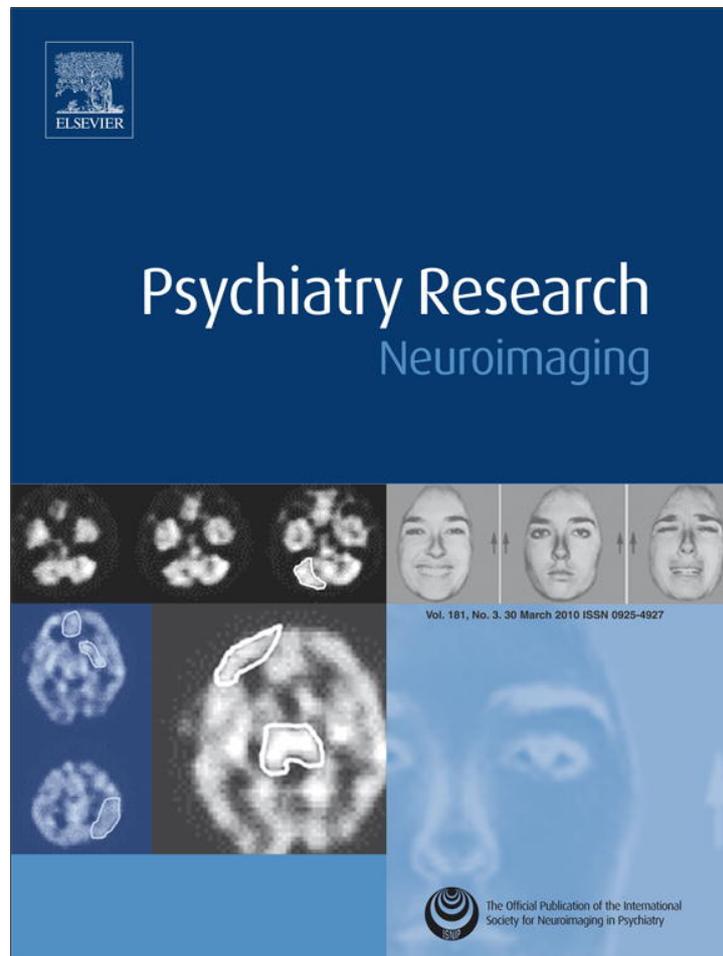


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Brief report

Medial prefrontal cortex hyperactivation during social exclusion in borderline personality disorder

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ABSTRACT

Frontal systems dysfunction and abandonment fears represent central features of borderline personality disorder (BPD). BPD subjects ($n = 10$) and matched non-psychiatric comparison subjects ($n = 10$) completed a social-cognitive task with two confederates instructed to either include or exclude subjects from a circumscribed interaction. Evoked cerebral blood oxygenation in frontal cortex was measured using 16-channel functional near infrared spectroscopy. BPD subjects showed left medial prefrontal cortex hyperactivation during social exclusion suggesting potential dysfunction of frontolimbic circuitry.

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1. Introduction

Borderline personality disorder (BPD) is a psychiatric condition characterized by a history of stormy and intense interpersonal relationships and hypersensitivity to rejection. Interpersonal dysfunction represents a core feature of BPD, although little is understood regarding its neurobiological substrate. Emerging evidence indicates that individuals with BPD show incapacity to maintain social cooperation and repair broken cooperative transactions, demonstrating a blunted response during cooperative exchanges in anterior insula, a region responsive to norm violations (King-Casas et al., 2008). Studies of affective processing in BPD provide additional clues about which neural systems may contribute to interpersonal dysfunction in this disorder. For instance, fMRI studies of BPD show less deactivation in amygdala and greater activation in superior temporal and frontal sulci when regulating responses to negative social cues (Koenigsberg et al., 2009), and decreased ventromedial prefrontal cortex activity is associated with behavioral inhibition in the context of negative emotion in BPD (Silbersweig et al., 2007). On the whole, functional neuroimaging studies of affective processing in BPD implicate a dysfunction of frontolimbic circuitry, possibly involving the medial prefrontal cortex (mPFC) specifically (for a

review, see New et al., 2008), although it remains unclear how these neural systems might mediate interpersonal functioning in BPD.

The mPFC is implicated in a variety of social-cognitive functions, most notably the processing of self-referential information and triadic interactions between two persons and an object (Saxe, 2006). The cytoarchitectonics of the frontal pole of mPFC and its inputs from the magnocellular portion of the mediodorsal thalamus argue for classification of this region as part of the orbitofrontal cortex (Kringelbach and Rolls, 2004), an area widely studied because of its role in personality (i.e., impulsivity). The mPFC is also thought to be principally involved in social-cognitive functions, including self-reflective processes and so-called “theory of mind” abilities (Satpute and Lieberman, 2006). Given the functional significance of this region for processes related to conceptualizations of the self and interactions with others, one might speculate that mPFC may play a central role in mediating the types of interpersonal difficulties characteristic of BPD.

The present study examines PFC function using a social-interpersonal paradigm in which two confederates are physically seated in a room with a subject and instructed to either include or exclude the subject from a circumscribed interpersonal interaction. The experimental paradigm is an adaptation of that presented in Eisenberger et al. (2003) using fMRI and a computerized task in which healthy subjects showed greater anterior cingulate cortex and right ventral PFC activity during social exclusion, the latter region thought to be involved in regulating the distress associated with social exclusion. We utilized functional near infrared spectroscopy (fNIRS) to measure brain activity because the technology is less

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sensitive to motion artifact compared with other imaging techniques (i.e., fMRI) and allows for continuous monitoring of cerebral blood oxygenation using a portable probe within an ecologically valid setting. The 16-channel fNIRS system implemented in the current protocol provides temporally precise measurements of blood oxygenation within regions restricted to PFC (Brodmann areas 9, 10, 45, and 46). In this context, we hypothesized that BPD subjects would show less right mPFC blood oxygenation compared to non-psychiatric comparison subjects during conditions of social exclusion, possibly suggesting a difficulty with top-down regulation of interpersonal and affective processes in BPD. These findings may shed light on the role of mPFC in social functions and illuminate the pathophysiology of interpersonal dysfunction in BPD.

2. Methods

2.1. Participants

The study received approval from the Drexel University Institutional Review Board. To be eligible to participate, all subjects met the following inclusion criteria: 18 years of age or older at the time of recruitment, female, English-speaking, right-handed, and able and willing to provide written informed consent. BPD subjects were required to meet DSM-IV criteria for current BPD based on the BPD module of the Diagnostic Interview for DSM-IV Personality Disorders (DIPD) (Zanarini et al., 1996). Subjects were ineligible for participation if they met DSM-IV criteria for schizophrenia or any psychotic disorder, bipolar disorder, current alcohol or substance use disorder, current eating disorder or lifetime eating disorder that required hospitalization, mental retardation, neurological or severe somatic disorder, or significant head trauma (>5 min loss of consciousness). Healthy subjects were excluded if they had a current diagnosis of any Axis I or Axis II disorder. In the week prior to testing, all subjects were instructed to abstain from cannabis or any other illicit drug use (urine drug screens unavailable), and severe alcohol consumption (i.e., intoxication). In addition, all subjects were instructed to abstain from coffee and nicotine 24 h prior to testing.

Ten females with BPD and 10 matched non-psychiatric comparison subjects provided written informed consent to participate in the study (see Table 1). They completed the BPD module of the DIPD and Structured Clinical Interview for DSM-IV Axis I Disorders (First et al., 1996) with collateral information was obtained from treating clinicians when available. All 10 BPD subjects endorsed the criterion of unstable interpersonal relationships and nine endorsed abandonment fears. BPD subjects additionally met criteria for major depressive disorder, recurrent ($n = 3$); social phobia ($n = 2$); dysthymic disorder ($n = 1$); and post-traumatic stress disorder ($n = 1$). Non-BPD personality disorder was measured dimensionally using the Minnesota Multiphasic Personality Inventory-2 personality disorder scales (Somwaru and Ben-Porath, 1995). BPD subjects scored higher on many of these scales (i.e., paranoid, schizotypal, antisocial, and avoidant) compared with healthy controls (all P 's < 0.001). Structured interviewing for assessment of non-BPD Axis II disorders was not completed for economic purposes. Three BPD subjects were currently receiving outpatient treatment: psychotherapy alone ($n = 1$), pharmacologic treatment alone ($n = 1$), and combined psychotherapy and pharmacologic treatment ($n = 1$). Subjects receiving pharmacologic treatment were taking stimulant ($n = 1$) and antipsychotic ($n = 1$) medications.

2.2. Procedures

Subjects were screened for inclusion and exclusion criteria and those who satisfied these criteria were invited to participate in the study. After providing written informed consent, subjects completed clinical assessments followed by neuroimaging procedures using a 16-channel fNIRS system. fNIRS is an optical brain imaging technique

Table 1

Demographic characteristics and self-report ratings during social exclusion task for borderline personality disorder (BPD) and healthy control subjects (HC).

	BPD	HC
<i>N</i>	10	10
Age ^a	22.1 (7.3)	19.0 (1.1)
Years of education ^b	13.2 (1.8)	12.9 (0.9)
Race/Ethnicity ^c		
Caucasian	8	8
African-American	0	1
Asian or Pacific Islander	2	1
Full scale IQ ^d	108.1 (13.1)	111.1 (9.2)
Pre-task ratings ^e		
Depression	3.44 (1.59)	1.40 (0.52)
Anxiety	3.89 (1.83)	2.60 (1.96)
Post-Inclusion ratings ^e		
Depression	2.67 (1.00)	1.22 (0.44)
Anxiety	3.33 (1.50)	2.67 (2.50)
Inclusiveness	8.56 (1.13)	8.80 (1.40)
Rejection	2.22 (.83)	1.20 (0.63)
Post-Exclusion ratings ^e		
Depression	3.33 (2.00)	1.67 (1.00)
Anxiety	3.78 (1.99)	2.78 (2.68)
Inclusiveness	2.89 (1.36)	2.60 (1.27)
Rejection	6.44 (2.65)	7.10 (1.79)

Note: All task ratings were completed using a scale ranging from 1 (not at all) to 10 (extremely severe).

^a $t(18) = -1.34, p = 0.20$.

^b $t(18) = -0.49, p = 0.63$.

^c $\chi^2(2) = 1.33, p = 0.51$.

^d $t(18) = -0.59, p = 0.56$.

^e All P 's > 0.05 (non-significant).

which allows for continuous monitoring of cerebral blood flow based on the differential absorption of infrared light in biological tissue. It is unique from fMRI in that it has greater temporal resolution (on the order of milliseconds) with less precise spatial resolution (centimeters). fNIRS provides measurements of oxygenated (oxy-Hb), deoxygenated, and total hemoglobin, whereas the fMRI blood-oxygen level dependent (BOLD) signal seems to be more highly correlated with fNIRS deoxygenated hemoglobin, and possibly total hemoglobin, parameters (Steinbrink et al., 2006). The technology is also advantageous because it is safe, non-invasive, and portable. The fNIRS system utilized in the present study was originally designed by Dr. Britton Chance at the University of Pennsylvania and further developed at the Drexel University School of Biomedical Engineering, Science, and Health Systems [see Irani et al. (2007) and Izzetoglu et al. (2004) for a review of fNIRS principles, instrumentation, and applications based on work from our laboratory.] The fNIRS probe was adhered to the subject's forehead over standard EEG positions F₇, F_{p1}, F_{p2}, and F₈. The four channels comprising the right and left mPFC were examined as regions-of-interest (ROI) based on the hypotheses presented above and the proposed relevance of mPFC to social-cognitive functioning and affective disturbance in BPD. Additional whole-probe analyses were conducted on the remaining 12 channels.

As previously mentioned, the neuroimaging paradigm was adapted from the computerized task described in Eisenberger et al. (2003), modified such that confederates were physically present with the subject and directly participated in the social interaction. The experiment started with the subject seated at a table with two confederates with a standard deck of 52 playing cards placed face-down at the center of the table. The subject was selected to begin the game and told to place one card face-down in front of any one player of their choosing. The rule was that only the player who had just received a card could take the next card and place it face-down in front of another player; no person could give herself or himself a card. Subjects were told that the player who received the card with the queen of hearts would receive a small token. Thus, the player with the most cards at the end of the game had the greatest chance of receiving this card. During the first scan ("Inclusion Condition"), subjects were

fully included in the social interaction with the other two players (i.e., cards were placed in front of the subject by the confederates), which continued until the full deck of cards was exhausted. In the second scan (“Exclusion Condition”), the subject received seven cards from the confederates and the subject was then completely excluded from the social interaction when the confederates stopped placing cards in front of the subject for the remainder of the scan (45 cards). Evoked oxy-Hb data from the final 30 s of the exclusion condition were used for fNIRS analyses. Subjects were initially asked to stare directly at the deck of cards placed at the center of the table for 10 s such that baseline fNIRS parameters could be established. Following each scan, subjects provided ratings of their feelings of inclusiveness and rejection during the previous scan. Initially and after each scan, subjects rated their current level of anxiety and depression. At the completion of the task, the deception was revealed and a debriefing protocol was implemented.

3. Results

3.1. Social exclusion task ratings

A main effect of Condition was found for inclusiveness, $F(1,18) = 193$, $P < 0.0001$, and rejection ratings, $F(1,18) = 196$, $P < 0.0001$, with subjects reporting higher levels of inclusiveness after the Inclusion Condition and higher levels of rejection during the Exclusion Condition. Thus, successful experimental manipulation of the target variables was confirmed. There was no main effect of Group or Group \times Condition interaction (all P 's > 0.05) (see Table 1).

3.2. Region-of-interest analyses

Mixed within-between analysis of variance within the ROI comprised of the four channels of mPFC revealed a significant main effect of Condition, $F(1,18) = 20$, $P < 0.001$, with higher levels of oxy-Hb in the Exclusion versus Inclusion condition. There was also a Group \times Condition interaction, $F(1,18) = 7.2$, $P = 0.015$, with BPD subjects demonstrating similar levels of evoked oxy-Hb compared with controls during the Inclusion condition, $t(18) = 0.32$, $P = 0.75$. During the Exclusion condition, however, BPD subjects showed higher levels of oxy-Hb relative to controls in left mPFC, $t(18) = -2.32$, $P = 0.03$ (see Fig. 1). This difference remained statistically significant after excluding subjects with current depression, $t(15) = -2.37$,

$P = 0.03$, and marginally significant when excluding subjects with current pharmacologic treatment, $t(15) = -2.10$, $P = 0.06$, although decreased power likely contributes to the latter finding given limited sample size. Correlation analysis revealed a significant association between oxy-Hb in left mPFC during the Exclusion condition and a dimensional rating of rejection and abandonment fears from the DIPD ($r = 0.49$, $P = 0.029$).

3.3. Whole-probe analyses

No differences in oxy-Hb between BPD and non-psychiatric comparison subjects during either the inclusion or exclusion conditions were observed in any of the remaining 12 channels (all P 's > 0.05).

4. Discussion

The mPFC is a region critical for managing social and interpersonal transactions (Saxe, 2006). Whereas a disruption of frontal systems is believed to play a central role in BPD (see Ruocco, 2005), few paradigms have been developed to characterize mPFC function during the course of an interpersonal interaction. The present study showed a higher prefrontal cortical response for BPD subjects relative to non-psychiatric comparison subjects in left mPFC/frontal pole under conditions of social exclusion. Furthermore, evoked oxygenation in this region was associated with clinical ratings of BPD-related rejection and abandonment fears. These findings are the first to implicate alterations of mPFC activity as a possible neurobiological substrate of interpersonal dysfunction in BPD.

The neurophysiologic basis of this mPFC hyperactivity remains unclear, particularly given that most studies have found decreased frontal activation in BPD, although similar findings have been reported in mood disorders, including bipolar disorder (Robinson et al., 2008) and major depression (Matsuo et al., 2007). The suggestion from fMRI studies of mood disorders is that prefrontal hyperactivity implies a disruption of frontolimbic circuitry, a finding which might be extended to inform the pathophysiologic mechanism of interpersonal dysfunction in BPD. The restriction of fNIRS to anterior regions of the frontal cortex, however, precluded investigation of potential subcortical limbic interactions with frontal systems in this study. The mPFC shares several reciprocal connections with limbic structures and it remains possible that prefrontal hyperactivity may play a role in modulating activity in structures such as the amygdala, which show increased activation to affective stimuli in BPD (New et al., 2008). Moreover, hyperactivation of mPFC during social exclusion may serve as a potential endophenotype of BPD, although replication and extension of these findings is necessary.

Some limitations should be noted as they relate to these findings. First, fNIRS has limited spatial resolution (i.e., centimeters) and depth of penetration (i.e., cortex), narrowing the scope of anatomic regions which can be studied. Second, the group of BPD subjects included in the present study was relatively young and drawn from the community and university counseling centers. Thus, these findings may not be typical of more ill patients with severe functional impairment. Third, the results of this study should be interpreted with caution given the potential influence of Axis I comorbidity and treatment status on these findings. Future studies using appropriate Axis I and Axis II comparison groups are necessary to determine the specificity of these results for BPD. Nevertheless, the results of the present study highlight the utility of ecologically valid functional neuroimaging procedures for exploring the neurocognitive substrates of interpersonal dysfunction in BPD.

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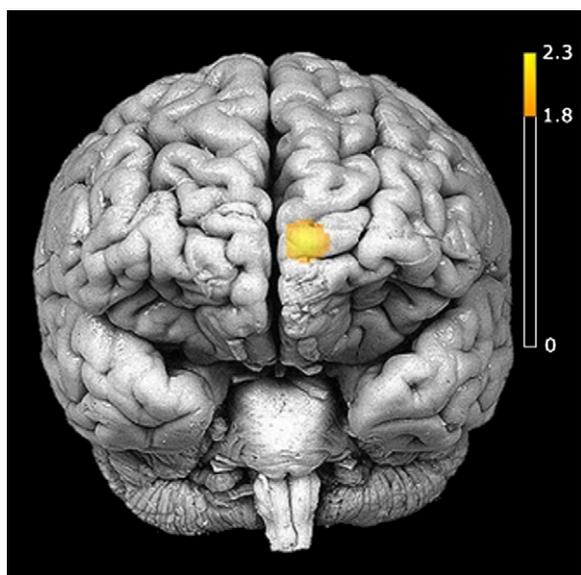


Fig. 1. Activation map showing hyperactivity of oxy-Hb in mPFC/frontopolar cortex for borderline personality disorder versus healthy controls during social exclusion.

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