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Electrocortical Reactivity During Self-referential Processing in Female Youth With Borderline Personality Disorder

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ABSTRACT

BACKGROUND: Borderline personality disorder (BPD) is debilitating, and theoretical models have postulated that cognitive-affective biases contribute to the onset and maintenance of BPD symptoms. Despite advances, our understanding of BPD pathophysiology in youth is limited. The present study used event-related potentials (ERPs) to identify cognitive-affective processes that underlie negative self-referential processing in BPD youth.

METHODS: Healthy females (n = 33) and females with BPD (n = 26) 13 to 22 years of age completed a self-referential encoding task while 128-channel electroencephalography data were recorded to examine early (i.e., P1 and P2) and late (late positive potential [LPP]) ERP components. Whole-brain standardized low-resolution electromagnetic tomography explored intracortical sources underlying significant scalp ERP effects.

RESULTS: Compared to healthy females, participants with BPD endorsed, recalled, and recognized fewer positive and more negative words. Moreover, unlike the healthy group, females with BPD had faster reaction times to endorse negative versus positive words. In the scalp ERP analyses, the BPD group had greater P2 and late LPP positivity to negative as opposed to positive words. For P2 and late LPP, whole-brain standardized low-resolution electromagnetic tomography analyses suggested that females with BPD overrecruit frontolimbic circuitry in response to negative stimuli.

CONCLUSIONS: Collectively, these findings show that females with BPD process negative self-relevant information differently than healthy females. Clinical implications and future directions are discussed.

Keywords: Borderline personality disorder, LPP, P1, P2, Self-referential processing, sLORETA

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The prevalence of borderline personality disorder (BPD) in adolescent community samples is approximately 1% (1–3). However, between 11% to 27% of outpatients (4,5) and 43% to 49% of inpatients (6) are believed to meet the diagnostic criteria for BPD during adolescence and young adulthood. Although BPD is more frequently diagnosed in females than males (7,8), epidemiologic data suggest that the lifetime prevalence of BPD among women and men is comparable (9). BPD in youth is characterized by greater nonsuicidal self-injury (10,11), and BPD severity has been found to predict suicide attempts (12). Although BPD has profound psychosocial and emotional consequences throughout the lifespan, research probing cognitive-affective processes underlying BPD in youth is limited.

Theoretical models in adult populations have postulated that cognitive biases contribute to the onset and maintenance of BPD symptoms (13–15), and these biases are particularly potent when processing negative self-relevant information. Indeed, BPD is marked by greater self-criticism (16), increased rejection sensitivity (17), more persistent shame (18), and negative emotion processing biases (19). Recently, Winter *et al.* (20) found that during a self-referential encoding task (SRET), adults with BPD judged positive and neutral self-relevant words as being more negative, and these negative self-referential processing biases—the tendency to appraise negative content as being related to one's own person—were correlated with a more dysfunctional attributional style. Converging evidence from neuroimaging studies has shown that BPD is characterized by potentiated activation to negative emotional information in paralimbic regions (21,22). To date, the majority of BPD research testing cognitive biases generally (and self-referential processing biases specifically) has been conducted in adults. Therefore, it is important to test whether self-referential processing biases are present in youth with BPD and to explore potential pathophysiologic mechanisms that may underlie these biases.

Event-related potentials (ERPs), which provide temporal resolution in the millisecond range, can offer a unique tool for probing brain mechanisms underlying self-referential biases. Early ERP components, such as the P1 and P2, are believed to reflect automatic processes, particularly to salient emotional information (23,24). The P1 (~100–200 ms post-stimulus) and P2 (~200–300 ms poststimulus) are maximal over parieto-occipital sites, and research has shown that there

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is differential activity after negative versus positive words among depressed individuals for the P1 (25) and P2 (26) components. These early effects suggest that lexical processing of emotional information occurs rapidly, and importantly, that these components are modulated by word valence (27–30).

The late positive potential (LPP), a slow-wave ERP component spanning several hundred milliseconds to seconds (31,32), indexes sustained engagement with emotional stimuli, including words (26,33) and images (34,35). Initially, the LPP is maximal over centroparietal sites (i.e., early LPP), but it also is evident in frontocentral sites later in the temporal course of the component (i.e., late LPP) (36). The frontal propagation may be particularly relevant to the current study in light of neuroimaging research implicating prefrontal cortex abnormalities during negative self-referential processing in patients with depression (25,37) and BPD (21,22,38,39). There is functional overlap between the early and late LPP; early LPP reflects encoding, retrieval, and processing of emotional information (40), and late LPP is thought to be more closely associated with memory storage and affective encoding (41).

Previous research testing self-referential processing biases in youth has primarily been examined in the context of depression (25,42–44). As a whole, this research has shown that compared to healthy adolescents, depressed youth are more likely to endorse and recall negative self-relevant information. In addition, depressed youth have a faster reaction time (RT) when endorsing negative self-relevant words and a slower RT during endorsement of positive words. Capitalizing on the time resolution of ERPs, Auerbach *et al.* (25) examined depressotypic self-referential processing biases by evaluating ERP components. When probing the P1, which reflects semantic monitoring of emotional information (23,45), depressed youth had greater P1 amplitudes after negative words, and greater P1 positivity to negative words was correlated with greater self-criticism and a more depressogenic self-view. For the LPP, depressed youth showed sustained positivity for negative versus positive words, and healthy youth showed the opposite effect. Collectively, these findings suggest that ERP activity may reinforce and intensify debilitating symptoms. Earlier findings highlighted shared clinical, etiologic, and pathophysiologic features between depression and BPD (17,46), and we hypothesized that similar findings would emerge when testing ERP components in youths with BPD.

Although BPD is characterized by a negative evaluation bias, research investigating behavioral and neural mechanisms underlying these deficits in youths with BPD is sparse. Therefore, the goal of this study is to identify pathophysiologic mechanisms that differentiate healthy and BPD female youth. BPD is more readily diagnosed in females relative to males (1,47), and we therefore focused on female youth in this initial study and tested the following hypotheses. First, in line with past research in adults with BPD (20), relative to healthy female youth, BPD participants will endorse, recall, and recognize more negative and fewer positive self-relevant words during an SRET. Moreover, BPD youth will have a faster RT to negative words and slower RT to positive words. Second, compared to healthy youth, those with BPD will show greater P1 and P2 positivity to negative versus positive words. Similarly, the BPD group also will show sustained positivity to negative versus positive words in the early and late LPP. Finally, standardized low-resolution electromagnetic tomography (sLORETA) whole-brain analyses were used to evaluate the potential intracortical contributors of significant scalp findings. In light of earlier neuroimaging evidence (22), we hypothesized that scans of females with BPD would be characterized by paralimbic hyperresponsiveness to negative self-referential stimuli.

METHODS AND MATERIALS

Participants

Our sample included female youths (healthy controls [HCs] = 33; females with BPD = 26) 13 to 22 years of age. Demographic and clinical characteristics are presented in Tables 1 and 2. The HC and BPD participants did not differ in terms of age or race. However, BPD youth reported a higher family income; as a result, family income was included as a covariate in all analyses. No healthy female participants used psychiatric medications, but females with BPD reported the following medication use: 1) 69.2% (n = 18) antidepressants (e.g., selective serotonin reuptake inhibitors and serotonin–norepinephrine reuptake inhibitors); 2) 57.7% (n = 15) atypical antipsychotics; 3) 34.6% (n = 9) mood stabilizers; 4) 19.2% (n = 5) atypical antidepressants; 5) 19.2% (n = 5) benzodiazepines; 6) 11.5% (n = 3) stimulants; and 7) 7.7% (n = 2) naltrexone. Of the original 59 participants, electroencephalography (EEG) data from 3 HCs were excluded because of poor quality of the data. The complete sample was used for behavioral analyses (HC = 33, BPD = 26).

Procedure

The Partners Institutional Review Board provided approval for the study. Assent was obtained from females 13 to 17 years of age, and signed consent was provided by participants ≥18 years of age and from the legal guardians of all minors. HCs were recruited from the community, whereas BPD participants were recruited through an intensive Dialectical Behavior Therapy (DBT) clinical program. Inclusion criteria included English fluency, female, and right-handedness. Exclusion criteria for the HCs included any history of psychiatric illness, psychotropic medication use, organic brain syndrome, neurologic disorders, or seizures. BPD participants had the same exclusion criteria with the exception of psychiatric history and psychotropic medication use. The study procedures were completed over 2 separate days. On the first study visit, participants were administered diagnostic interviews probing Axis I and II psychopathology and completed self-report instruments regarding symptom severity. During the second study visit, EEG data were acquired while participants completed an SRET. The majority of study visits were completed within the same week (mean, 3.51 days [standard deviation, 4.09]), and participants were remunerated $50.

Instruments

Diagnostic Assessments. Participants were administered clinical interviews by bachelor's-level research assistants,

Table 1. Clinical and Demographic Data Among Healthy Controls and Youths With Borderline Personality Disorder

			Statistics	
	HC (n = 33)	BPD (n = 26)	t/χ^2	p
Mean Age, Years (SD)	17.39 (3.16)	16.96 (1.82)	0.66	.51
Mean BPD Symptoms[a] (SD)	0.67 (0.92)	14.27 (7.38)	–9.34	<.001
Mean Depressive Symptoms[b] (SD)	0.82 (1.89)	30.72 (11.75)	–12.84	<.001
Ethnicity, n (%)			1.82	.77
White	22 (66.7)	19 (73.1)		
Asian	6 (18.2)	4 (15.4)		
Multiple races	3 (9.1)	3 (11.5)		
Black	1 (3.0)	0 (0.0)		
Other	1 (3.0)	0 (0.0)		
Income, n (%)			19.42	.002
≥$100,000	16 (48.5)	25 (96.2)		
$75,000–$100,000	7 (21.2)	0 (0)		
$50,000–$75,000	6 (18.2)	0 (0)		
$25,000–$50,000	2 (6.1)	0 (0)		
$10,000–$25,000	2 (6.1)	1 (3.8)		

BPD, borderline personality disorder; HC, healthy control.
[a]Zanarini Rating Scale for Borderline Personality Disorder.
[b]Beck Depression Inventory-II.

graduate students, and postdoctoral fellows. All interviewers received approximately 50 hours of training, which included didactics, listening to past interviews, role play, mock interviews, and direct oversight. In addition, clinical recalibration meetings were regularly conducted. To assess Axis I disorders, participants were administered the Mini International Neuropsychiatric Interview for Children and Adolescents [MINI-KID (48)]. The MINI-KID is a brief, structured diagnostic interview that assesses current Axis I psychopathology in youth. Research has shown good reliability and validity in community (48) and psychiatric (49) samples. Participants also were administered the Structured Clinical Interview for DSM-IV Axis II Personality Disorders, BPD module [SCID-II BPD (50)]. The SCID-II BPD module is a semistructured clinical interview. All BPD diagnoses received external confirmation from the BPD participant's primary psychiatrist or psychotherapist. Only BPD participants who both met criteria during the SCID-II assessment and received an independent confirmatory diagnosis from the primary psychiatrist or psychotherapist participated in the study.[1]

Table 2. Comorbidity for Youths With Borderline Personality Disorder (n = 26)

Comorbidity	n (%)
Major Depressive Disorder/Dysthymia	21 (80.8)
Substance Disorder	10 (38.5)
Social Phobia	9 (34.6)
Attention-Deficit/Hyperactivity Disorder	8 (30.8)
Posttraumatic Stress Disorder	6 (23.1)
Bipolar II Disorder/Bipolar Disorder NOS	5 (19.2)
Generalized Anxiety Disorder	5 (15.4)
Agoraphobia	4 (15.4)
Obsessive-Compulsive Disorder	4 (15.4)
Panic Disorder	4 (15.4)
Specific Phobia	2 (7.7)
Bulimia Nervosa	1 (3.8)
Psychotic Disorder	1 (3.8)

NOS, not otherwise specified.

Symptom Severity. The Zanarini Rating Scale for Borderline Personality Disorder [ZAN-BPD (51)] is a 9-item self-report instrument assessing BPD psychopathology. Item scores range from 0 to 4, and greater total scores indicate greater BPD severity. The Cronbach's alpha in the current sample was 0.92, indicating strong internal consistency. The Beck Depression Inventory–II [BDI-II (52)] is a 21-item self-report questionnaire assessing depressive symptom severity over the past 2 weeks. Items ranged from 0 to 3, and higher scores are indicative of greater depression severity. In the current study, the Cronbach's alpha was 0.97, indicating excellent internal consistency.

Experimental Task

The SRET included 80 trials consisting of 40 positive and 40 negative adjectives (25). Adjectives were selected from the Affective Norms for English Words based on criteria including

[1]When study recruitment began, there was no criterion standard for assessing BPD diagnoses in adolescents. In part, a diagnosis of BPD in adolescents became more commonplace after the release and publication of the DSM-5 (61). However, at the start of our study, there was no universally agreed upon clinical instrument to use with adolescents <18 years of age. To ensure the reliability of our diagnosis for all participants, we used the SCID-II clinical interview and also verified this diagnosis with the participants' primary psychiatrist or psychotherapist.

valence, arousal, frequency, and length (53).[2] Positive and negative stimuli were significantly different in valence (t_{79} = –55.88, $p < .001$); however, there were no statistical differences when comparing arousal ($t_{79} = 0.68$, $p = .50$), frequency ($t_{79} = -1.64$, $p = .11$), or word length ($t_{79} = -0.06$, $p = .95$). Stimuli were pseudorandomly presented, with no more than two words of the same valence shown in succession. The stimuli was presented for 200 ms, followed by a fixation cross (1800 ms), and the participant was then presented with a question prompt ("Does this word describe you?"). Participants responded by pressing "Yes" or "No" on a button box. Intertrial intervals were jittered between 1500 and 1700 ms. Before the start of the task, participants completed three practice trials using affectively neutral words. Data collection was initiated when the participant was ready. After completing the 80 trials, participants were asked to count backward from 50. After this brief distractor, participants completed a surprise recall task and then were administered a recognition task that included 160 words (80 original adjectives, 80 matched distractors).

EEG Recording, Data Reduction, and Analysis

The EEG was recorded using a 128-channel HydroCel GSN Electrical Geodesics, Inc. (Eugene, OR) net, and continuous EEG data, referenced to the Cz, were sampled at 250 Hz. EEG electrode impedances were kept <50 to 75 kΩ and offline analyses were performed using BrainVision Analyzer 2.04 software (Brain Products, Gilching, Germany). EEG data were rereferenced to the average reference, and offline filters (0.1–30 Hz) were applied. To identify and remove eye movement artifacts and eye blinks, an independent component analysis transform was implemented. For each trial, EEG data were then segmented 200 ms before and 1200 ms after stimulus onset. A semiautomated procedure to reject intervals for individual channels used the following criteria: 1) a voltage step >50 μV between sample rates, 2) a voltage difference >300 μV within a trial, and 3) a maximum voltage difference of <0.50 μV within a 100-ms interval. All trials also were visually inspected for manual artifact rejection.

ERPs were computed time-locked to all available positive and negative words, whereby the average amplitude 200 ms before the stimulus served as a baseline. Next, ERP amplitudes were examined at sensor locations equivalent to selected electrodes in the 10/10 system. Scalp location and start/end of time windows of interest were consistent with previous research using the same self-referential tasks (25). The P1, P2, and early LPP components were calculated as the mean area across electrode sites CPz, Pz, CP1, and CP2, for the following time windows: 1) P1, 100–200 ms, 2) P2, 200–300 ms, and 3) early LPP, 300–600 ms. The late LPP was examined across the average of frontocentral midline electrode sites Fz, FCz, and Cz and operationalized as the average area in the 600 to 1200 ms poststimulus time window.

For behavioral (i.e., word endorsement, reaction time, recall, and recognition) and ERP (i.e., P1, P2, and LPP) analyses,[3] SPSS software (version 20.0; SPSS, Inc, Chicago, IL) was used to conduct a series of 2-way mixed analyses of covariance with group (i.e., HC and BPD) and condition (i.e., positive words and negative words) as factors. General linear model software using the Greenhouse–Geisser correction was applied.[4] We used a Bonferroni correction to adjust for the inflated familywise error rate in the post hoc tests for within or between comparisons, and our critical alpha was set to $p < .025$.

sLORETA

sLORETA (54) estimated intracerebral current density underlying significant scalp effects. Current density was computed as the linear weighted sum of the scalp electric potentials at each voxel ($N = 6239$; voxel resolution = 5 mm^3) for specified poststimulus time windows. The sLORETA solution space is limited to cortical gray matter and hippocampi, as defined by the Montreal Neurological Institute (MNI305) template. For each participant, sLORETA values were normalized to a total power of 1 and then log-transformed (log 10) before analyses. A $p = .005$ threshold with a minimum cluster size of 5 voxels was used to minimize type II errors.

RESULTS

Descriptive Statistics

Clinical and demographic statistics are summarized in Tables 1 and 2. Correlations among symptoms, behavioral indicators, and ERPs are summarized in Table 3. When

[2]The following positive ($n = 40$) and negative ($n = 40$) words were included in the self-referential encoding task (in alphabetical order): admired, adorable, afraid, alive, alone, angry, anguished, beautiful, bold, bored, bright, brutal, burdened, capable, carefree, confident, cruel, crushed, cute, defeated, depressed, devoted, dignified, disgusted, disloyal, displeased, distressed, dreadful, elated, engaged, famous, fearful, festive, friendly, frustrated, gentle, grateful, guilty, happy, helpless, honest, hopeful, hostile, insane, insecure, inspired, jolly, joyful, lively, lonely, lost, loyal, lucky, masterful, morbid, obnoxious, outstanding, proud, rejected, rude, satisfied, scared, shamed, silly, sinful, stupid, surprised, terrible, terrific, terrified, thoughtful, troubled, unhappy, untroubled, upset, useful, useless, vigorous, violent, and wise.

[3]Lateralization effects were tested, but no significant differences were found.

[4]Although the high degree of collinearity might speak against the use of a covariate that captures depression severity, we reran all 2-way mixed analyses of covariance with group (i.e., HC and BPD) and condition (i.e., positive words and negative words) as factors testing the group × condition interaction for behavioral and ERP effects while controlling for current depressive symptoms (and family income given the group difference). Despite the robust correlation between BPD and depression symptoms ($r = .87$, $p < .001$), there were significant interaction effects for word endorsement ($p = .004$) and recognition ($p = .02$); RT ($p = .08$) and recall ($p = .06$) effects trended in the expected direction. For the ERP analyses, the interaction effects no longer remained significant ($p = .37$–$.98$), which might not be surprising given the high degree of collinearity between depressive and BPD symptom severity.

Table 3. Correlations Among Symptoms, Behavioral Indices, and Event-Related Potentials

	1	2	3	4	5	6	7	8	9	10
Positive Words										
1. BPD symptoms	—									
2. Depression symptoms	0.87[a]	—								
3. Endorse	−0.67[b]	−0.79[a]	—							
4. Reaction time	0.04	0.001	−0.07	—						
5. Recall	−0.21	−0.31[c]	0.23	−0.06	—					
6. Recognition	−0.08	−0.03	0.07	−0.16	0.38[b]	—				
7. P1	−0.18	−0.11	0.02	−0.09	0.12	0.14	—			
8. P2	−0.18	−0.17	−0.002	−0.07	0.27[c]	−0.02	0.60[a]	—		
9. Early LPP	−0.42[b]	−0.38[b]	0.35[b]	−0.16	0.12	0.08	0.44[a]	0.49[a]	—	
10. Late LPP	−0.10	−0.09	0.01	0.01	−0.04	0.03	0.12	0.26	0.32[c]	—
Negative Words										
1. BPD symptoms	—									
2. Depression symptoms	0.87[a]	—								
3. Endorse	0.83[b]	0.90[a]	—							
4. Reaction time	−0.27	−0.32[c]	−0.35[c]	—						
5. Recall	0.21	0.21	0.30[c]	−0.13	—					
6. Recognition	0.39[b]	0.47[a]	0.50[a]	−0.26	0.45[a]	—				
7. P1	0.14	0.12	0.09	0.004	0.09	−0.02	—			
8. P2	0.04	0.02	0.04	0.05	0.20	−0.02	0.62[a]	—		
9. Early LPP	−0.09	−0.09	−0.11	0.25	0.17	0.004	0.14	0.38[b]	—	
10. Late LPP	−0.04	−0.09	−0.06	−0.19	−0.06	0.12	0.23	0.35[b]	0.44[b]	—

BPD, borderline personality disorder; LPP, late positive potential.
Healthy adolescents (n = 16) who did not endorse any negative words as self-relevant were excluded from reaction time correlations.
[a]$p < .001$.
[b]$p < .01$.
[c]$p < .05$.

examining behavioral and ERP effects, a significant correlation emerged for words endorsed and the early LPP. Notably, greater endorsement of positive words was associated with more sustained early LPP positivity, and enhanced P2 positivity after positive words was associated with greater recall of positive words. Neither RT nor recognition was associated with ERPs.

Behavioral Data

Behavioral data from the SRET are summarized in Table 4.

Words Endorsement. The group × condition interaction was significant ($F_{1,56}$ = 148.98, $p < .001$, η_p^2 = .73). Between-group comparisons revealed that female youths with BPD endorsed fewer positive words ($p < .001$, η_p^2 = .57) and more negative words ($p < .001$, η_p^2 =.77) relative to female HCs.

Reaction Time. If a participant did not endorse any negative or positive words as being self-relevant, data were only excluded from the RT analysis (16 HCs did not endorse any negative words). As hypothesized, the group × condition interaction was significant ($F_{1,40}$ = 7.14, p = .01, η_p^2 = .15). Post hoc between-group analyses revealed no difference in RT for positive words (p = .73, η_p^2 = .003), but females with BPD were significantly faster endorsing self-relevant negative words (p = .01, η_p^2 = .17).

Free Recall. A significant group × condition interaction emerged ($F_{1,56}$ = 18.86, $p < .001$, η_p^2 = .25). Between-group analyses showed that female youths with BPD free-recalled fewer positive words relative to healthy participants (p = .002, η_p^2 = .16). There were no differences in negative words (p = .23, η_p^2 = .03).

Recognition. There was a significant group × condition interaction ($F_{1,56}$ = 38.07, $p < .001$, η_p^2 = .41). No difference emerged for positive words (p = .37, η_p^2 = .01). Interestingly, female youths with BPD recognized more negative words compared to HCs ($p < .0001$; η_p^2 = .20).

Event-Related Potentials

For the P1, the main effect for group ($F_{1,53}$ = 0.12, p = .91, η_p^2 < .001) was not significant. While the group × condition interaction ($F_{1,53}$ = 2.69, p = .07, η_p^2 = .06) was not significant, it trended in the expected direction. When examining the P2, the main effect for group was not significant ($F_{1,53}$ = 0.01, p = .91, η_p^2 < .001). However, as hypothesized, a significant group × condition interaction emerged ($F_{1,53}$ = 4.38, p = .04, η_p^2 = .08). No between-group effects emerged for positive (p = .48, η_p^2 = .01) or negative (p = .63, η_p^2 = .004) words. However, within-group effects found that participants with BPD showed greater positivity for negative versus positive words (p = .03, η_p^2 = .09); no

Table 4. Behavioral Data for the Self-referential Encoding Task

	HC (n = 33)		BPD (n = 26)	
Task	Mean	SD	Mean	SD
Endorse				
Positive	31.61	5.73	14.92	8.42
Negative	1.21	1.83	22.69	8.80
Reaction Time[a]				
Positive	517.40	191.25	513.60	309.50
Negative	990.10	1042.21	452.06	169.21
Recall				
Positive	10.70	3.18	7.77	3.35
Negative	6.61	3.62	7.92	4.39
Recognition				
Positive	33.52	3.41	32.62	4.43
Negative	27.79	5.72	33.00	4.67

BPD, borderline personality disorder; HC, healthy control.
[a]Measured in milliseconds.

within-group effect emerged in the HCs (p = .44, η_p^2 = .01; see Figure 1).

With respect to the early LPP, there was no main effect for group ($F_{1,53}$ = 1.92, p = .17, η_p^2 = .04) or group × condition interaction ($F_{1,53}$ = 2.62, p = .11, η_p^2 = .05). When examining the late LPP mean area, no group main effect emerged ($F_{1,53}$ = 0.15, p = .70, η_p^2 = .003). There was, however, a significant group × condition interaction ($F_{1,53}$ = 9.57, p = .003, η_p^2 = .15). Post hoc analyses revealed that the HCs had sustained positivity for positive versus negative words (p = .05, η_p^2 = .07), although this did not survive the Bonferroni correction. BPD participants showed the opposite effect (p = .02, η_p^2 = .11; Figure 2). These within-group findings emerged within the context of no between-group differences for positive (p = .36, η_p^2 = .02) or negative (p = .13, η_p^2 = .04) words.

sLORETA

Whole-brain sLORETA group × condition analyses (p = .005 threshold with a minimum cluster size of 5 voxels) during the P2 and late LPP were examined, but no significant interactions emerged (P2: $p > .24$; LPP: $p > .15$). BPD is characterized by aberrant reactivity to negative stimuli (19,20), and therefore exploratory between-group analyses tested whole-brain differences during the P2 and late LPP after negative words (Table 5, Figure 3). For the P2, compared to the HCs, youths with BPD had greater current density to negative words in the inferior temporal gyrus, medial temporal gyrus, cingulate gyrus, and postcentral gyrus. Subjects with BPD showed similar effects during the late LPP within the postcentral and precentral gyrus after negative words.

DISCUSSION

The present study examined negative self-referential processing biases in female youth diagnosed with BPD, and several important findings emerged. First, compared to healthy youths, patients with BPD endorsed, recalled, and recognized more negative and fewer positive self-relevant words. In addition, youth with BPD were faster to endorse negative words as being self-relevant. Second, for the P2 and late LPP, females with BPD showed greater positivity after negative versus positive words, and HCs showed the opposite effect. Although the P1 trended in the expected direction, the early LPP effect was not significant. Finally, consistent with previous imaging research in adults with BPD (22,38), sLORETA analyses indicated that female BPD youth may be overrecruiting frontolimbic circuitry during the presentation of negative self-relevant stimuli.

Consistent with existing research in this area (20), our behavioral findings showed that females with BPD had a negative self-referential processing bias with medium to large effect sizes. Although cognitive-affective biases are believed to play a causal role in BPD onset in adults (6,13), research examining negative self-referential processing biases in female youths with BPD is scarce. Negative self-referential processing biases are pernicious, and for some may potentiate key symptoms that characterize BPD in youth. Selectively attending to negative self-relevant material may contribute to the development of a negative self-image (e.g., feeling damaged or deficient) that fosters feelings of emptiness and hopelessness. In addition, youths with BPD often have a prominent fear of abandonment. As these youths selectively attend to negative self-relevant information, it may further entrench maladaptive schemas pertaining to being unlovable and worthless. Once activated, these schemas trigger beliefs that females with BPD will ultimately be rejected and abandoned. Perhaps not surprisingly, interventions (e.g., DBT) aimed at challenging these dysfunctional biases reduce BPD severity in youth (55).

Building on previous research, our study showed that early and late scalp-recorded ERPs may underlie negative self-referential processing biases in female youths with BPD. Although P1 effects trended in the expected direction, group differences did not emerge. This finding is unexpected given previous work with depressed adolescents (25); however, the P1 does not always emerge when probing self-referential processes, even in occipital electrode sites (45,56). When testing the P2, females with BPD showed greater ERP reactivity to negative versus positive words, and the HCs showed the opposite effect with a small effect size. This effect appears to be driven by within-group differences in BPD youth showing greater positivity to negative versus positive words and is largely consistent with research in depressed adults (26). Although group differences did not emerge for the early LPP, the number of positive words endorsed was associated with early LPP positivity. This relationship may reflect sustained engagement for self-relevant adjectives. For late LPP, females with BPD showed larger (more positive) LPP positivity for negative versus positive words (medium effect size), and the healthy group showed the opposite effect. Collectively, these findings have two implications. First, our results suggest that discrete neural processes may be contributing to self-referential processing biases among female youths with BPD. Second, potentiated ERP reactivity to negative self-relevant words may reflect greater emotional salience to negative self-relevant information (28,45). There was no association between the LPP and RT, and this likely reflects sustained engagement as opposed to motor preparation. Over time, it

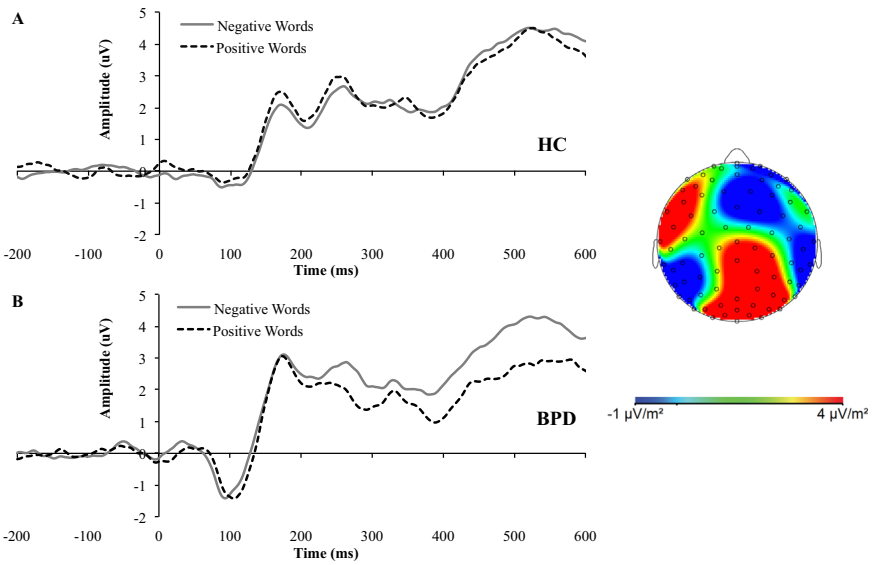

Figure 1. Electrocortical activity for the P1, P2, and early late positive potential. P1, P2, and early late positive potential electrocortical activity in response to positive and negative words averaged across electrode sites CPz, Pz, CP1, and CP2 for **(A)** healthy controls (HC) (n = 30) and **(B)** female youth with borderline personality disorder (BPD) (n = 26). Scalp topographies reflect the average topography of positive and negative words across participants 200–300 ms poststimulus.

may result in increased intensity and severity of BPD symptoms.

Exploratory analyses conducted with sLORETA found that compared to HCs, individuals with BPD overrecruit frontolimbic circuitry in the presence of negative self-relevant information. Broadly speaking, this pattern of hyperactivation is consistent with neuroimaging research conducted in adults with BPD (21,22,38). In a study with BPD participants using near infrared spectroscopy, adults with BPD showed hyperactivation in the left medial prefrontal cortex during social exclusion trials. These alterations within the medial prefrontal cortex are believed to represent a core dysfunction in BPD (39). Interestingly, self-referential processing biases have been linked to hypoactivation in frontolimbic circuitry among depressed adolescents (25,37,57), suggesting that differential activation may contribute to negative self-referential processing biases in patients with BPD as opposed to depressed individuals. At the same time, it is important to acknowledge that our findings emerged in the absence of a group × condition interaction.

Limitations

Findings should be interpreted in light of several limitations. First, although comorbidity in patients with BPD is commonplace (58), particularly with depression, it may impact our ability to detect behavioral and ERP effects that are specific to BPD. Indeed, when controlling for depression severity, ERP

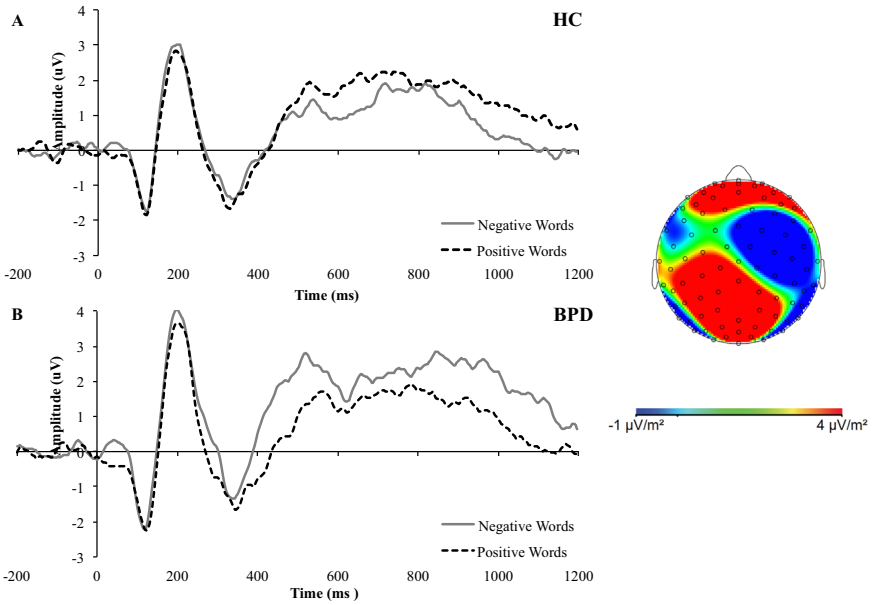

Figure 2. Electrocortical activity for late late positive potential. Late late positive potential electrocortical activity in response to positive and negative words averaged across electrode sites FCz, Fz, and Cz for **(A)** healthy controls (HC) (n = 30) and **(B)** female youth with borderline personality disorder (BPD) (n = 26). Scalp topographies reflect the average topography of positive and negative words across participants 600–1200 ms poststimulus.

Table 5. Standardized Low-Resolution Brain Electromagnetic Tomography Whole-Brain Analyses During the P2 (200–300 ms) and Late LPP (600–1200 ms) After Negative Words

Region	Brodmann Areas	Time Frame Poststimulus (ms)	MNI Coordinates X	Y	Z	Voxels	*t* Value
Inferior Temporal Gyrus	20, 21	200–300	–50	0	−40	11	–3.18
Medial Frontal Gyrus	6, 9	200–300	10	30	35	7	–3.68
Postcentral Gyrus	2, 3, 40	200–300	–35	–25	50	27	–3.41
Cingulate Gyrus	5, 7, 31	200–300	–50	45	5	15	–3.03
Postcentral Gyrus (Left)	2, 40	600–1200	–55	–35	55	12	–3.61
Postcentral Gyrus (Right)	2, 40	600–1200	40	–35	55	12	–3.47
Precentral Gyrus	2, 3, 6	600–1200	–35	–30	65	23	–3.72

BPD, borderline personality disorder; HC, healthy control; LPP, late positive potential.

Negative *t* values reflect greater current density in BPD (n = 26) relative to HC (n = 30) female youths in contiguous voxels thresholded at p = .005. X = left (–) to right (+); Y = posterior (–) to anterior (+); Z = inferior (–) to superior (+).

effects no longer remained significant. In addition, given the psychiatric complexity of the BPD sample, the majority of these youth were medicated. Some research suggests that psychotropic medication normalizes neural dysfunction in individuals with BPD (22). In our study, medication use may have masked some group differences; yet behavioral and electrocortical findings emerged despite BPD medication use. Second, pubertal status was not assessed. The brain undergoes dynamic change pre- to postpuberty, which may impact electrocortical processes. Third, the study is cross-sectional, and we cannot ascertain whether the significant behavioral and ERP effects are cause or consequence of BPD. Fourth, we could not explicitly examine ERPs associated with endorsed self-relevant adjectives. In part, healthy adolescents endorsed few negative words, and adolescents with BPD did not endorse a sufficient number of positive adjectives (Table 4). Fifth, clinical interviews were not audiotaped, which precluded us from obtaining interrater reliability. Nonetheless, BPD diagnoses were confirmed with the primary clinician, and frequent recalibration meetings were held to ensure reliability of diagnoses. No other Axis II disorders were assessed. Finally, data were acquired using a 128-channel net from Hydro-Cel GSN EGI, which provides rapid application, but higher impedances are common.

Clinical Implications and Future Directions

The National Institute of Mental Health has highlighted the importance of precision medicine—providing targeted treatment based on specific patient characteristics (59). One possibility for future research may be to determine whether there are baseline predictors, such as electrocortical reactivity, that predict response to cognitive-oriented therapies (e.g., DBT). Although neuroprediction is challenging, there is an increasing precedent for using brain connectomics to predict outcome response (60). Alternatively, it is unclear whether aberrant neurobiologic activity normalizes in treatment. Future research in this area may facilitate the development of adjunctive treatments. Taken together, these lines of research may improve the treatment of patients with BPD.

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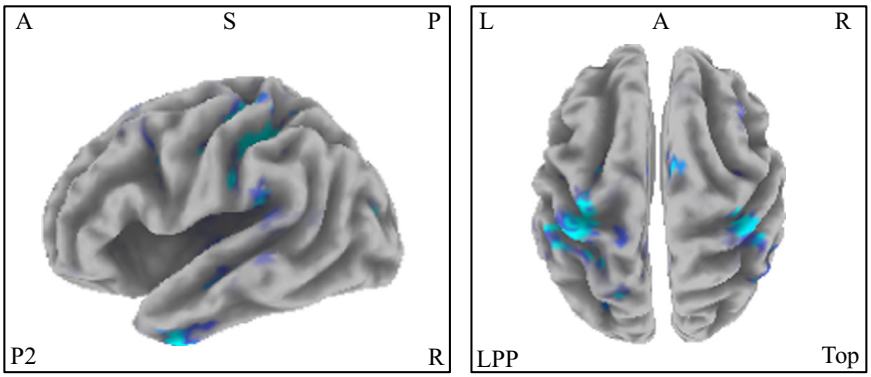

Figure 3. Standardized low-resolution electromagnetic tomography contrasts for healthy controls (n = 30) and female youth with borderline personality disorder (n = 26) after negative words. Results of independent *t* tests contrasting healthy controls with female youths with borderline personality disorder after negative words in the self-referential encoding task (blue: borderline personality disorder > healthy controls) for the P2 (left) and late LPP (right). Statistical maps are thresholded at p = .005. A, anterior; L, left; LPP, late positive potential; P, posterior; R, right; S, superior.

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REFERENCES

1. Torgersen S, Kringlen E, Cramer V (2001): The prevalence of personality disorders in a community sample. Arch Gen Psychiat 58: 590–596.
2. Samuels JF, Nestadt G, Romanoski AJ, Folstein MF, McHugh PR (1994): DSM-III personality disorders in the community. Am J Psychiat 151:1055–1062.
3. Johnson DM, Shea MT, Yen S, Battle CL, Zlotnick C, Sanislow CA, *et al*. (2003): Gender differences in borderline personality disorder: Findings from the Collaborative Longitudinal Personality Disorders Study. Compr Psychiat 44:284–292.
4. Chanen AM, Jackson HJ, McGorry PD, Allot KA, Clarkson V, Yuen HP (2004): Two-year stability of personality disorder in older adolescent outpatients. J Pers Disord 18:526–541.
5. Ha C, Balderas JC, Zanarini MC, Oldham J, Sharp C (2014): Psychiatric comorbidity in hospitalized adolescents with borderline personality disorder. J Clin Psychiat 75:e457–e464.
6. Levy KN, Becker DF, Grilo CM, Mattanah JJ, Garnet KE, Quinlan DM, *et al*. (1999): Concurrent and predictive validity of the personality disorder diagnosis in adolescent inpatients. Am J Psychiat 156: 1522–1528.
7. Gunderson JG, Zanarini MC (1987): Current overview of the borderline diagnosis. J Clin Psychiat 48:5–14.
8. Swartz M, Blazer D, George L, Winfield I (1990): Estimating the prevalence of borderline personality disorder in the community. J Pers Disord 4:257–272.
9. Grant BF, Chou SP, Goldstein RB, Huang B, Stinson FS, Saha TD, *et al*. (2008): Prevalence, correlates, disability, and comorbidity of DSM-IV borderline personality disorder: Results from the Wave 2 National Epidemiologic Survey on Alcohol and Related Conditions. J Clin Psychiat 69:533–545.
10. Nock MK, Joiner Jr TE, Gordon KH, Lloyd-Richardson E, Prinstein MJ (2006): Non-suicidal self-injury among adolescents: Diagnostic correlates and relation to suicide attempts. Psychiat Res 144:65–72.
11. Muehlenkamp JJ, Ertelt TW, Miller AL, Claes L (2011): Borderline personality symptoms differentiate non-suicidal and suicidal self-injury in ethnically diverse adolescent outpatients. J Child Psychol Psyc 52:148–155.
12. Jacobson CM, Muehlenkamp JJ, Miller AL, Turner JB (2008): Psychiatric impairment among adolescents engaging in different types of deliberate self-harm. J Clin Child Adolesc 37:363–375.
13. Blatt SJ, Luyten P (2009): A structural-developmental psychodynamic approach to psychopathology: Two polarities of experience across the life span. Dev Psychopathol 21:793–814.
14. Bornstein RF, Becker-Matero N, Winarick DJ, Reichman AL (2010): Interpersonal dependency in borderline personality disorder: Clinical context and empirical evidence. J Pers Disord 24:109–127.
15. Levy KN, Edell WS, McGlashan TH (2007): Depressive experiences in inpatients with borderline personality disorder. Psychiat Quart 78: 129–143.
16. Kopala-Sibley DC, Zuroff DC, Russell JJ, Moskowitz DS, Paris J (2012): Understanding heterogeneity in borderline personality disorder: Differences in affective reactivity explained by the traits of dependency and self-criticism. J Abnorm Psychol 121:680–691.
17. Gunderson JG (2007): Disturbed relationships as a phenotype for borderline personality disorder. Am J Psychiat 164:1637–1640.
18. Rusch N, Lieb K, Gottler I, Hermann C, Schramm E, Richter H, *et al*. (2007): Shame and implicit self-concept in women with borderline personality disorder. Am J Psychiat 164:500–508.
19. Izurieta Hidalgo NA, Oelkers-Ax R, Nagy K, Mancke F, Bohus M, Herpertz SC, *et al*. (2016): Time course of facial emotion processing in women with borderline personality disorder: An ERP study. J Psychiatry Neurosci 41:16–26.
20. Winter D, Herbert C, Koplin K, Schmahl C, Bohus M, Lis S (2015): Negative evaluation bias for positive self-referential information in borderline personality disorder. PloS One 10:e0117083.
21. van Zutphen L, Siep N, Jacob GA, Goebel R, Arntz A (2015): Emotional sensitivity, emotion regulation and impulsivity in borderline personality disorder: A critical review of fMRI studies. Neurosci Biobehav Rev 51:64–76.
22. Schulze L, Schmahl C, Niedtfeld I (2016): Neural correlates of disturbed emotion processing in borderline personality disorder: A multimodal meta-analysis. Biol Psychiat 79:97–106.
23. Kissler J, Herbert C, Winkler I, Junghofer M (2009): Emotion and attention in visual word processing: An ERP study. Biol Psychol 80: 75–83.
24. West WC, Holcomb PJ (2000): Imaginal, semantic, and surface-level processing of concrete and abstract words: An electrophysiological investigation. J Cogn Neurosci 12:1024–1037.
25. Auerbach RP, Stanton CH, Proudfit GH, Pizzagalli DA (2015): Self-referential processing in depressed adolescents: A high-density event-related potential study. J Abnorm Psychol 124:233–245.
26. Shestyuk AY, Deldin PJ (2010): Automatic and strategic representation of the self in major depression: Trait and state abnormalities. Am J Psychiat 167:536–544.
27. Huang YX, Luo YJ (2006): Temporal course of emotional negativity bias: An ERP study. Neurosci Lett 398:91–96.
28. Ortigue S, Michel CM, Murray MM, Mohr C, Carbonnel S, Landis T (2004): Electrical neuroimaging reveals early generator modulation to emotional words. Neuroimage 21:1242–1251.
29. Flor H, Knost B, Birbaumer N (1997): Processing of pain- and body-related verbal material in chronic pain patients: Central and peripheral correlates. Pain 73:413–421.
30. Knost B, Flor H, Braun C, Birbaumer N (1997): Cerebral processing of words and the development of chronic pain. Psychophysiology 34: 474–481.
31. Friedman D, Johnson R (2000): Event-related potential (ERP) studies of memory encoding and retrieval: A selective review. Microsc Res Tech 51:6–28.
32. Hajcak G, Olvet DM (2008): The persistence of attention to emotion: Brain potentials during and after picture presentation. Emotion 8: 250–255.
33. Fischler I, Bradley M (2006): Event-related potential studies of language and emotion: Words, phrases, and task effects. Prog Brain Res 156:185–203.
34. Foti D, Hajcak G (2008): Deconstructing reappraisal: Descriptions preceding arousing pictures modulate the subsequent neural response. J Cogn Neurosci 20:977–988.
35. Weinberg A, Hajcak G (2011): The late positive potential predicts subsequent interference with target processing. J Cogn Neurosci 23: 2994–3007.
36. Foti D, Hajcak G, Dien J (2009): Differentiating neural responses to emotional pictures: Evidence from temporal-spatial PCA. Psychophysiology 46:521–530.
37. Lemogne C, Mayberg H, Bergouignan L, Volle E, Delaveau P, Lehericy S, *et al*. (2010): Self-referential processing and the prefrontal cortex over the course of depression: A pilot study. J Affect Disord 124: 196–201.
38. New AS, Goodman M, Triebwasser J, Siever LJ (2008): Recent advances in the biological study of personality disorders. Psychiatr Clin North Am 31:441–461.
39. Ruocco AC, Medaglia JD, Tinker JR, Ayaz H, Forman EM, Newman CF, *et al*. (2010): Medial prefrontal cortex hyperactivation during social exclusion in borderline personality disorder. Psychiat Res 181: 233–236.
40. Naumann E, Bartussek D, Diedrich O, Laufer ME (1992): Assessing cognitive and affective information processing functions of the brain by means of the late positive complex of the event-related potential. J Psychophysiol 6:285–298.
41. Ruchkin DS, Johnson Jr R, Mahaffey D, Sutton S (1988): Toward a functional categorization of slow waves. Psychophysiology 25: 339–353.

42. Connolly SL, Abramson LY, Alloy LB (2015): Information processing biases concurrently and prospectively predict depressive symptoms in adolescents: Evidence from a self-referent encoding task. Cogn Emot 30:550–560.
43. Timbremont B, Braet C (2004): Cognitive vulnerability in remitted depressed children and adolescents. Behav Res Ther 42:423–437.
44. Zupan BA, Hammen C, Jaenicke C (2007): The effects of current mood and prior depressive history on self-schematic processing in children. J Exp Child Psychol 43:149–158.
45. Kissler J, Herbert C, Peyk P, Junghofer M (2007): Buzzwords: Early cortical responses to emotional words during reading. Psychol Sci 18: 475–480.
46. Beeney JE, Levy KN, Gatzke-Kopp LM, Hallquist MN (1991): EEG asymmetry in borderline personality disorder and depression following rejection. Personal Disord 5:178–185.
47. Widiger TA, Weissman MM (1991): Epidemiology of borderline personality disorder. Hosp Community Psych 42:1015–1021.
48. Sheehan DV, Sheehan KH, Shytle RD, Janavs J, Bannon Y, Rogers JE, *et al*. (2010): Reliability and validity of the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID). J Clin Psychiat 71:313–326.
49. Auerbach RP, Millner AJ, Stewart JG, Esposito EC (2015): Identifying differences between depressed adolescent suicide ideators and attempters. J Affect Disord 186:127–133.
50. First MB, Spitzer RL, Gibbon M, Williams JBW (1995): The structured clincial inteview for DSM-III-R personality disorders (SCID-II). Part I: Description. J Pers Disord 9:83–91.
51. Zanarini MC, Vujanovic AA, Parachini EA, Boulanger JL, Frankenburg FR, Hennen J (2003): Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD): A continuous measure of DSM-IV borderline psychopathology. J Pers Disord 17:233–242.
52. Beck AT, Steer RA, Brown GK (1996): Beck Depression Inventory Manual, *2nd ed.* San Antonio, TX: Psychological Corporation.
53. Bradley MM, Lang PJ (2010): Affective norms for english words (ANEW): Stimuli, instruciton manual, and affective ratings (tehcnical report C-2). Gainsville, FL: The Center for Research in Psychophysiology, University of Florida.
54. Pascual-Marqui RD (2002): Standardized low-resolution brain electromagnetic tomography (sLORETA): Technical details. Methods Find Exp Clin Pharmacol 24:5–12.
55. Groves S, Backer HS, van den Bosch W, Miller A (2012): Review: Dialectical behaviour therapy with adolescents. Child Adolesc Mental Health 17:65–75.
56. Herbert C, Junghofer M, Kissler J (2008): Event related potentials to emotional adjectives during reading. Psychophysiology 45:487–498.
57. Mayberg HS (1997): Limbic-cortical dysregulation: a proposed model of depression. J Neuropsych Clin N 9:471–481.
58. Zanarini MC, Frankenburg FR, Dubo ED, Sickel AE, Trikha A, Levin A, *et al*. (1998): Axis I comorbidity of borderline personality disorder. Am J Psychiatry 155:1733–1739.
59. Insel TR (2014): The NIMH Research Domain Criteria (RDoC) Project: Precision medicine for psychiatry. Am J Psychiatry 171:395–397.
60. Whitfield-Gabrieli S, Ghosh SS, Nieto-Castanon A, Saygin Z, Doehrmann O, Chai XJ, *et al*. (2016): Brain connectomics predict response to treatment in social anxiety disorder. Mol Psychiatry 21:680–685.
61. American Psychiatric Association (2013): Diagnostic and Statistical Manual of Mental Disorders, *5th ed.* Washington, DC: American Psychiatric Press.