



Short communication

Short communication: Diffusion tensor anisotropy in the cingulate in borderline and schizotypal personality disorder



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ABSTRACT

Despite considerable phenomenological differences between borderline personality disorder (BPD) and schizotypal personality disorder (SPD), research increasingly provides evidence that some BPD symptoms overlap with SPD symptoms (e.g., disturbed cognitions). We examined the cingulate, a brain region implicated in the pathophysiology of both disorders, to determine similarities/differences between the groups, and similarities/differences from healthy controls (HC's). 3T structural and diffusion tensor magnetic resonance imaging scans were acquired in BPD ($n = 27$), SPD ($n = 32$), HC's ($n = 34$). Results revealed that BPD patients exhibited significantly lower FA in posterior cingulate white matter compared to HC's ($p = 0.04$), but SPD patients did not.

1. Introduction

Borderline personality disorder (BPD) is characterized by affective instability and impulsive behavior (Gunderson and Singer, 1975; Kernberg, 1977). Schizotypal personality disorder (SPD), on the other hand, is characterized by symptoms of odd behavior, magical thinking, social anxiety, and paranoid ideation. As such, emotion dysregulation is among the primary symptoms used to diagnose BPD, whereas disturbed cognition constitutes one of the primary criteria for diagnosing SPD. Despite these nosological differences between the two disorders, research increasingly provides evidence of BPD difficulty with symptoms that are typically associated with SPD (e.g., odd thinking, non-delusional paranoia) (Farsham et al., 2017; Rawlings et al., 2001; Zanarini et al., 2013), which may result, at least in part, from similar neurobiological underpinnings.

The current study aimed to investigate neurobiological factors contributing to the aforementioned aspects of BPD that may overlap with and/or diverge from aspects of SPD. It examined the integrity of the cingulate, a functionally heterogeneous brain region frequently implicated in the affective symptomatology of BPD and in the cognitive symptomatology of SPD. Specifically, it aimed to examine gray and

white matter cingulate structural integrity among three groups: healthy controls (HC) vs. BPD individuals without comorbid SPD vs. SPD individuals without comorbid BPD.

The cingulate consists of several functionally distinct subdivisions that help modulate many of the functions with which both BPD and SPD individuals experience difficulty. Specifically, the anterior cingulate is divided into affect- and cognition-related sections; the ventral division plays a large role in emotion processing, and its dorsal division is thought to be involved in a number of cognitive functions, including modulation of attention/executive functions, motivation, and motor control (Bush et al., 2000). The posterior cingulate also has been implicated in areas of cognition, as well as in aspects of social functioning (Kennedy et al., 2006; Ochsner et al., 2005; Vogt et al., 1992). As such, given its involvement in these wide-ranging aspects of functioning, several of which constitute areas of weakness for BPD and/or SPD individuals—both shared and disorder-specific—the cingulate is thought to provide an ideal backdrop against which to compare these disorders. Specifically, the current study sought to investigate the integrity of these functionally distinct subdivisions of the cingulate to help clarify overlapping/differing neurobiological abnormalities across patient groups. Further, due to research reporting cingulate gray and white

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matter volumetric abnormalities in both of these groups and their potential relation to overlapping/diverging symptomatology (Hazlett et al., 2005), this study aimed to expand upon those findings by comparing other aspects of these cingulate subdivisions in these groups, namely diffusion-related measures of cingulate white and gray matter structure using diffusion tensor MRI (DTI).

DTI is one of the primary methodologies used to examine the orientation and microstructural integrity of brain tissue. DTI measures the motion of water molecules in tissues, which then is used to infer their microarchitecture (Taylor et al., 2004). Empirical studies have employed several different DTI quantitative measurements, including but not limited to fractional anisotropy (FA; measure of anisotropy of a diffusion process), axial diffusivity (AD; measure of parallel diffusivity), and radial diffusivity (RD; measure of perpendicular diffusivity).

To date, few DTI studies have been conducted in SPD and BPD. One of the first DTI studies reported lower fractional anisotropy (FA) in the uncinate fasciculus in SPD but found no SPD-HC group differences in the cingulate gyrus (Nakamura et al., 2005). Similarly, our group's more recent investigation of white matter integrity in the cingulum bundle in SPD patients did not find a group difference from HC's (Lener et al., 2015). Four prior DTI studies have examined the integrity of the cingulate in BPD (Lischke et al., 2015; Ninomiya et al., 2018; Rusch et al., 2010; Whalley et al., 2015). One of these studies examined FA in the anterior and posterior sections separately, reporting reduced FA in the anterior portion of the cingulum in BPD (Whalley et al., 2015). A separate investigation (Lischke et al., 2015) examined FA, axonal anisotropy, and radial diffusivity in the cingulum but did not find HC-BPD group differences.

Given the aforementioned findings, as well as increased studies reporting altered gray matter structural integrity using DTI in other populations (Li et al., 2018), the current study examined FA in both white and gray matter in the cingulate. It was hypothesized that altered FA would be detected in the affect-related ventral portion of the anterior cingulate in BPD patients because affective symptomatology has traditionally represented a core feature of the disorder. In SPD patients, it was hypothesized that altered FA would be detected in the cingulate subdivisions thought to subservise certain cognitive and social skills because both domains consistently have been highlighted as primary areas of SPD weakness.

2. Methods

2.1. Participants

Overall, 93 participants were included. Participants were recruited through local newspaper advertisements and clinical referral. Table 1 contains all demographic specifics. Also of note, we have previously published fMRI BOLD data in this sample (Hazlett et al., 2012). Group

Table 1
Demographics of study sample.

| Variable | BPD(n = 27) | SPD(n = 32) | HC(n = 34) | Test statistic |
|--------------|-------------|-------------|------------|--------------------------|
| Age (years): | 31.5(9.4) | 34.9(10.0) | 31.8(9.1) | F(2,90)=1.2, p = 0.3 |
| Range: | 18–51 | 20–55 | 22–56 | |
| Education: | 4.8(2.7) | 4.4(1.9) | 5.4(2.8) | F(2,78)=1.1, p = 0.3 |
| Gender: | | | | |
| Men | 12(44%) | 20(63%) | 18(53%) | $\chi^2(2)=1.9, p = 0.4$ |
| Women | 16(56%) | 12(37%) | 16(47%) | |

Note. BPD = Borderline Personality participants. SPD = Schizotypal. Personality Disorder participants. HC = Healthy Control participants. Education = Highest Degree Earned. 1 = No High School Diploma; 2 = GED; 3 = High School Diploma; 4 = Technical Training; 5 = Some College, No Degree;

6 = Associate Degree; 7 = Bachelor's Degree; 8 = Master's Degree; 9 = MD/PhD/JD/PharmD. *p < 0.05 (2-tailed).

differences in age, education, and gender were assessed using Student t-tests and chi-square, and there were no significant differences.

2.2. Materials and procedures

All eligible participants were administered the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-IV) (First et al., 1996) and the Structured Interview for DSM-IV Personality Disorders (SIDP) (Pfohl et al., 1997). Two self-report ratings were administered to assess affective symptomatology, Affective Liability Scale (ALS) (Harvey et al., 1989) and Affective Intensity Measure (AIM) (Larsen and Diener, 1987). Given the study's objective to parse out differences between BPD and SPD patients, none of the BPD patients met criteria for a comorbid diagnosis of SPD and none of the SPD patients met criteria for a comorbid diagnosis of BPD, making it a unique sample. That is, all patients met DSM-IV criteria for either BPD or SPD, but none met full criteria for both. However, BPD patients were allowed to have a sub-threshold number of SPD traits, and BPD patients were permitted to have a sub-threshold number of SPD traits to maintain external validity. Specifically, in diagnosing patients, each of the DSM-IV criteria for each personality disorder was rated on a 4-point scale (0 = absent, 0.5 = somewhat present, 1.0 = definitely present/prototypic, 2.0 = severe, pervasive). As required for a DSM-IV diagnosis of SPD, these patients met at least five of the nine SPD criteria with a rating ≥ 1.0 . SPD patients were allowed no more than three BPD criteria with two items rated as 1.0 and one item rated as 0.5 in order to control for comorbidity and/or co-occurring traits but still maintain external validity. As required for a DSM-IV diagnosis of BPD, these patients met at least five of the nine DSM-IV criteria. BPD patients were allowed no more than three SPD criteria with two items rated as 1.0 and one item rated as 0.5.

All participants were unmedicated at the time of their MRI scan (>6 weeks). Participants with a history of schizophrenia, psychotic disorder, bipolar (Type I) disorder, or current major depressive disorder (episode occurring within 2 months of the scan) were excluded. Exclusion criteria also included severe medical or neurological illness, head injury, or alcohol/substance dependence or alcohol/substance abuse during the prior six months. All participants had a negative urine toxicology screen for drugs of abuse during the study's screening visit and on the day of the MRI. Healthy control participants had no Axis I or II diagnosis and no Axis I disorder in any first-degree family member. All participants provided written informed consent in accordance with the Mount Sinai School of Medicine Institutional Review Board guidelines.

2.3. Image acquisition and processing

MRI acquisition for all participants occurred on a Siemens Allegra 3T-head-dedicated MRI system to acquire axial structural images and DTI using a pulsed-gradient spin-echo sequence with Echo Planar Imaging pulse sequence (EPI) acquisition (Segal et al., 2010). A b-factor of 1250 was chosen based on tests performed to find the optimal balance for SNR and diffusion weighting. Twelve gradient directions with $b = 1250 \text{ s/mm}^2$ were used (TR = 4100 ms, TE = 80 ms, FOV = 21 cm, matrix = 128×128 , 28 slices, thickness = 3 mm, skip = 1 mm). To solve the components of the diffusion tensor, 13 diffusion EPI images were obtained: 12 with different, non-coplanar and non-coplanar gradient encoding directions and one with no diffusion gradient applied. Five acquisitions were averaged to improve the signal-to-noise ratio. The tool 'eddy' was used to correct the diffusion-weighted images for distortions and head movement. The diffusion tensor was obtained by solving the 13 simultaneous signal equations relating the measured signal intensity to the diffusion tensor (Basser et al., 1994; Papadakis et al., 1999). This resulted in a tensor for every voxel ($1.6 \times 1.6 \times 3 \text{ mm}^3$) in a slice. The eigenvectors and eigenvalues were then computed for every tensor, forming the raw dataset for

analysis. For image quality control, radiofrequency inhomogeneities were screened for with a cylindrical water-filled phantom. All scans were inspected upon completion for motion artifacts and repeated if necessary. An axial 3D-MPRage image (TR = 2500 ms, TE = 4.4 ms, FOV = 21 cm, matrix size = 256×256 , 208 slices with thickness = 0.82 mm) was also obtained.

FA was used to determine the degree of diffusion anisotropy in each voxel. The anisotropy and eigenvector maps derived from the imaging data were computed off-line using in-house developed software that utilized SPM Matlab (Matlab v6.5, The Mathworks, Inc., Natick, MA). All scans were resectioned along the AC-PC line, and diffusion scans were coregistered to the anatomical MR images using FSL (FMRIB, Oxford, UK) after signal averaging for FA calculations. After DTI/T1 coregistration, region of interest coordinates were applied to the DTI scan of each individual. The FSL program FAST (Zhang et al., 2001) was then used to segment the MRI into gray and white matter and cerebrospinal fluid (CSF) with bias field correction of MRIs followed by k means clustering and local Markov analysis at each voxel. This was done such that a binary image was created for each of the three tissue types, and these coordinates were applied to the corresponding DTI image.

2.4. Cingulate tracing on MRI

The left and right anterior and posterior cingulate were traced on axial MR images. First, the cingulate gyrus was outlined on each subject's MP-RAGE structural MRI. The entire cingulate gyrus was also outlined on contiguous axial MRI slices for each subject (blind to diagnosis) and inter-tracer reliability was confirmed with Dr. Haznedar (inter-observer intraclass correlation coefficient for the anterior cingulate = 0.85 and posterior cingulate = 0.84). Methods have been published in detail elsewhere (Haznedar et al., 2000; Segal et al., 2010). Given the known heterogeneity of cingulate gyrus function and white matter structure, comparisons of mean FA for the entire gyrus may not be representative of potential localized changes due to BPD and SPD, respectively. Also, Brodmann's areas (BAs; Brodmann and Gary, 2006) cannot be reliably identified on MRI. As such, to determine mean FA for each region of the cingulate, the anterior cingulate was divided into six equal axial segments and the posterior cingulate into two segments (Fig. 1) on the basis of proportions derived from the Talairach–Tournoux atlas (Talairach and Tournoux, 1988). With this approach, it was possible to determine the volumes of each subunit of the anterior and posterior cingulate and measure their FA separately. T1 and DTI images were then coregistered for FA calculations.

2.5. Data analytic plan

Volumes were expressed relative to whole brain volume. A mixed-factorial design MANOVA was conducted with Diagnostic group as the categorical predictor (HC vs. SPD vs. BPD). For the cingulate analyses, repeated measures included hemisphere (left, right), segment (1–8 from anterior to posterior, Fig. 1) and tissue type (gray, white). Whole brain volume was used as a covariate for the FA analyses. The multivariate F Wilks is reported for all analyses ($p < 0.05$). All significant interactions with Diagnostic group were followed up with Fisher's LSD to determine the direction of the effect. Pearson's correlation coefficients (Bonferroni corrected) were used to examine associations between FA and ALS/AIM variables.

3. Results

All data were analyzed for normality using the Kolmogorov-Smirnov test of normality. The whole brain volume did not differ significantly among the groups (one-way ANOVA, $F(2,90) = 1.8$, $p \geq 0.2$, (means: HC $1,596,017 \pm 163,120.0 \text{ mm}^3$; BPD $1,534,582 \pm 115,304.9 \text{ mm}^3$; SPD $1,545,330 \pm 124,819.1 \text{ mm}^3$). Examinations of cingulate volume

showed that there was a significant interaction of group and tissue type related to volume [MANOVA (Diagnostic group x Tissue type) $F(2, 90) = 3.6$, $p = 0.03$, Wilks (Fig. 1)]. *Post-hoc* Fisher's LSD tests revealed that SPD patients had significantly smaller relative white matter volume compared with HC's ($p < 0.01$), and BPD patients showed significantly smaller relative white matter volume compared with HC's ($p = 0.03$). BPD patients displayed significantly smaller relative gray matter volume compared with HC's ($p = 0.04$). The patient groups did not differ from each other on relative gray or white matter volume, and none of the other interactions with diagnostic group were significant, ($p \geq 0.20$).

Given the significant between-group difference in volume, a MANCOVA was conducted to determine differences in FA among the three diagnostic groups, using overall brain volume as the covariate. There was no main effect of group ($p > 0.8$), but a Diagnostic group x Segment x Tissue type interaction effect on FA was significant (MANCOVA, $F(14, 166) = 1.8$, $p = 0.04$, Wilks). Compared with HC's, the BPD patients had lower FA in a segment of the posterior cingulate white matter (segment 2 of posterior cingulate; approximately BA 23; Fisher's LSD, $p = 0.04$). Also, relative to HC, BPD patients demonstrated lower FA in a segment of the anterior cingulate white matter (segment 4 of anterior cingulate; approximately BA's 24, 24', 33) that trended towards significance (Fisher's LSD, $p = 0.08$). None of the other interactions were significant, (p 's > 0.2). Further, a significant difference in the FA of cingulate gray and/or white matter was not detected between SPD patients and HC's, nor was a difference detected between BPD patients and SPD patients, (p 's > 0.05). Of note, all of the aforementioned analyses were also conducted using age as a second covariate, and the interaction results were consistent.

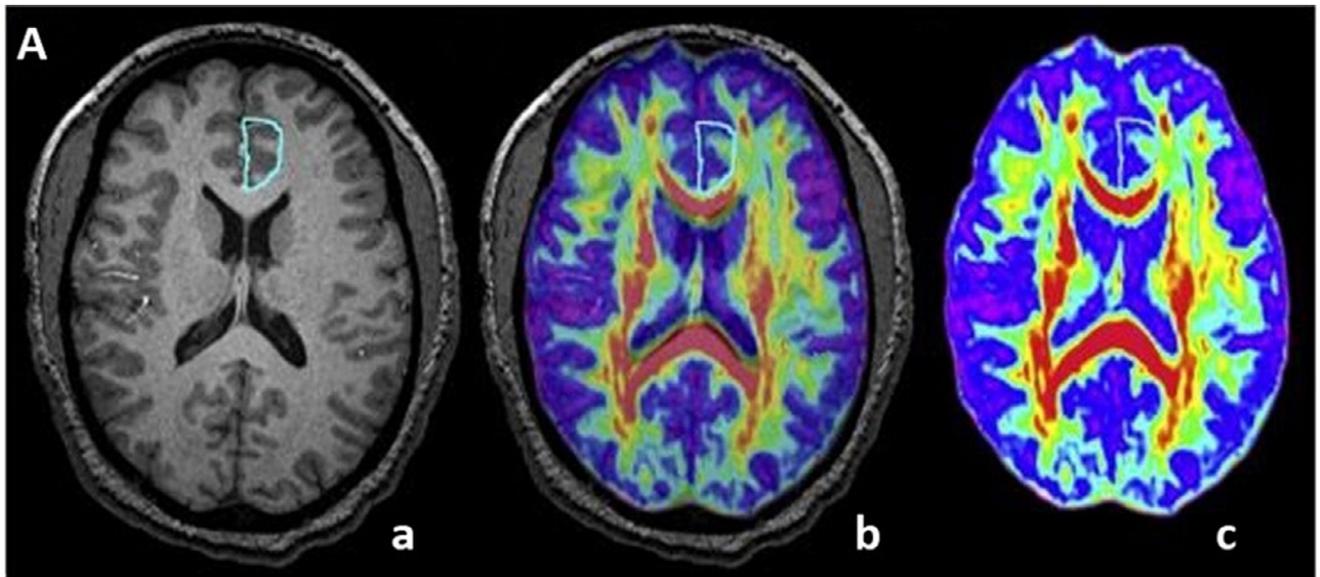
Pearson's correlations were calculated to examine the association between clinical symptomatology and FA in brain regions where patient groups showed FA differences from HC's. None of the correlations were statistically significant, (p 's > 0.10).

4. Discussion

Although some prior DTI studies have been published on individuals with BPD and SPD, this is the first DTI study to directly compare these diagnostic groups with one another and with HC's. The primary finding suggests that the overall pattern of white matter FA differs significantly between groups. Further, results reveal that the HC's and individuals with BPD differ most in the posterior region of the cingulate white matter.

In this respect, it is possible to interpret these findings within the context of results from functional neuroimaging studies reporting that BPD patients demonstrate abnormal activation and glucose metabolic patterns in posterior cingulate while performing cognitive tasks with emotional stimuli (Beblo et al., 2006a; Niedtfeld et al., 2012; Ruocco et al., 2013). Findings also can be understood within the context of research investigating the role of posterior cingulate in socio-emotional cognition (Torta and Cauda, 2011). Further, research has reported posterior cingulate involvement in the process of enabling new learning and motivating adaptive change in cognition and behavior (Heilbronner et al., 2013; Pearson et al., 2011), skills that may certainly relate to disturbed thought processes and behaviors in BPD.

Methodological limitations must be acknowledged. While the overall three-way interaction with diagnostic group was found to be statistically significant, the *post hoc* analyses were only significant with Fisher's LSD. Thus, the current findings need to be interpreted with caution. Also of note, given the study's moderate sample size and negative findings of altered cingulate integrity in SPD patients, future work should aim to include larger samples. Additionally, subsequent research should also examine correlations with affective/cognitive symptomatology, as the current study's negative correlation findings could certainly be due to small sample size but may also suggest that the detected cingulate abnormalities may be more related to trait-like



Axial MRI, left ACG outlined

Fused Image

FA Map

B

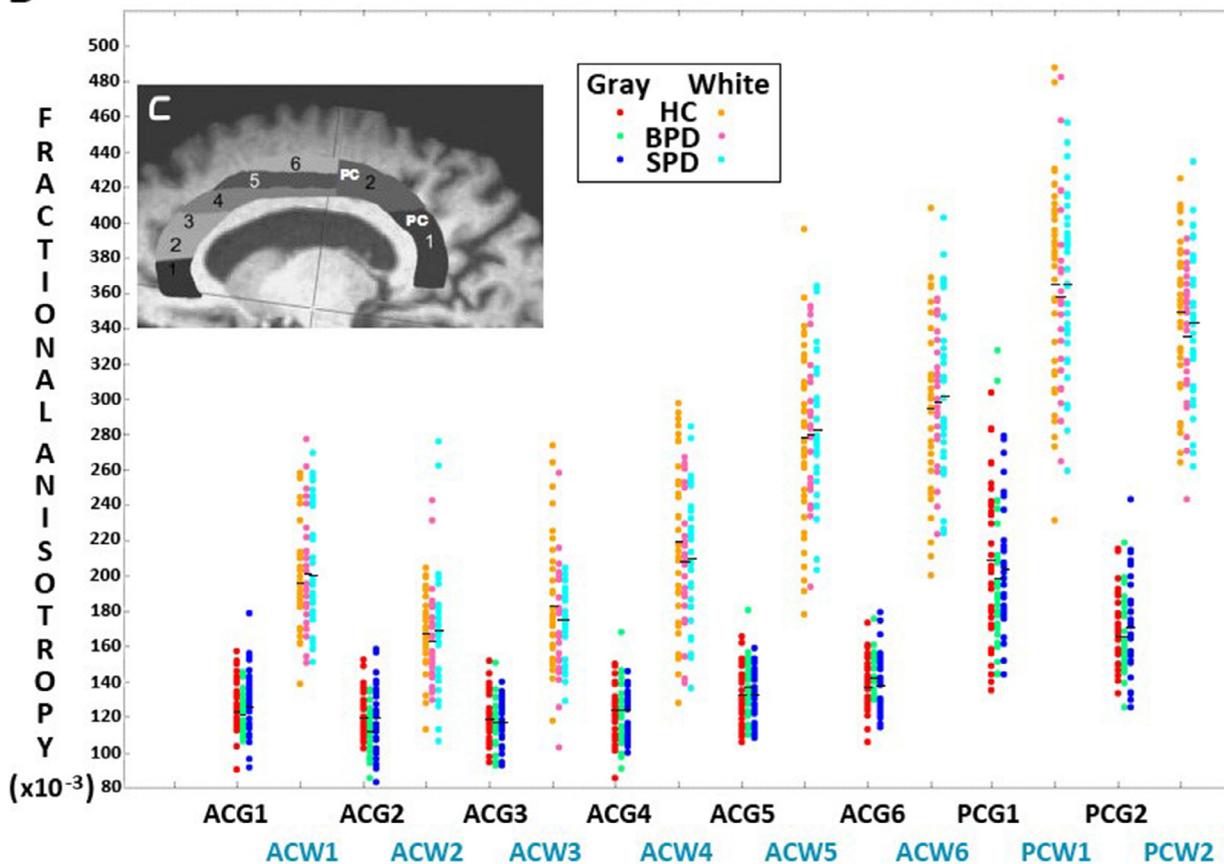


Fig. 1. A. Depiction of Co-registration of Anisotropy Map with the T1-weighted Image. **B.** Fractional Anisotropy Values in Cingulate Gray and White matter by Diagnostic Group, averaged over hemisphere. **C.** Sagittal Depiction of Cingulate Divided into Axial Segments.

Fig. 1A: Note. a: axial MRI image with the left anterior cingulate gyrus traced. b: fused image showing the co-registration of the anisotropy map with the T1-weighted image. c: FA map obtained with diffusion tensor acquisition. The color scale depicts FA values, as the highest FA values are seen in the corpus callosum and intermediate values are seen in the cingulum bundle.

Fig. 1B: Note. ACG = Anterior Cingulate Gray Matter; ACW = Anterior Cingulate White Matter; PCG = Posterior Cingulate Gray Matter; PCW = Posterior Cingulate White Matter.

Fig. 1C. Note. Anterior segments one through six constitute anterior cingulate; posterior segments one and two constitute posterior cingulate.

factors rather than affective state factors. Finally, although the patients and HC participants were matched on gender, the study's decreased number of women in the SPD patient group and decreased number of men in the BPD patient group did not allow for analysis of gender differences. This should be examined in future work given reports of prevalence differences across gender in these patient groups (Busch et al., 2016; Gawda et al., 2017).

In summary, the current findings extend the work of other studies that report on reduced white matter integrity in frontal regions and fiber tracts that connect frontal regions in adults with BPD and temporal regions in adolescents with BPD (Carrasco et al., 2012; Grant et al., 2007; New et al., 2013; Ninomiya et al., 2018; Rusch et al., 2010, 2007). It is consistent with prior research reporting BPD cingulate abnormalities and suggests the potential involvement of cingulate in BPD weaknesses, both affective and cognitive in nature. It also underscores the importance of utilizing treatment modalities that directly address BPD difficulties. For example, the finding of BPD alterations in aspects of the cingulate known to subservise error-monitoring abilities provide support for the use of dialectical behavior therapy and its mindfulness module, which work to help the individual stay in the present moment as well as improve the ability to make adaptive changes in cognition and behavior.

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