DIFFUSION TENSOR ANISOTROPY IN THE CINGULUM IN BORDERLINE AND SCHIZOTYPAL PERSONALITY DISORDER

A Dissertation
Submitted to
the Temple University Graduate Board

In Partial Fulfillment of the
Requirements for the Degree
DOCTOR OF PHILOSOPHY

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January 2014

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ABSTRACT

Borderline personality disorder (BPD) and schizotypal personality disorder (SPD) are both characterized by inflexible and pervasive behavioral patterns that frequently lead to significant functional impairment. Although considerable research has been conducted on the biological and phenotypic aspects of these disorders, researching, diagnosing, and treating them remains a challenge, primarily due to the difficulties associated with the categorical nature of current diagnostic methods (Skodol and Bender, 2009) which, in turn, results in significant within-group heterogeneity and between-group co-occurrence. Given the relative paucity of research comparing aspects of these disorders with one another, the current study aimed to evaluate overlapping and differentiating aspects of BPD and SPD by examining the integrity of a brain region frequently implicated in both disorders, the cingulum. The current study used a 3T Siemens scanner to acquire structural and diffusion tensor imaging in age-, sex-, and education-matched groups of 28 adults with BPD, 32 adults with SPD, and 36 healthy control participants (HC). The anterior and posterior cingulate were manually traced on all participants and then volume and fractional anisotropy (FA) comparisons were conducted across the groups for the left and right anterior and posterior cingulate. Compared with HC, SPD patients had smaller relative cingulate white matter volume and BPD patients had marginally significantly smaller relative cingulate white matter volume, and the two patient groups did not differ from one another. With regard to FA findings, a spectrum pattern emerged, such that the BPD group had significantly lower FA in the posterior cingulum relative to controls, whereas the SPD group also had lower FA in this region but did not differ from HC. The

BPD group had marginally lower FA in dorsal aspects of the anterior cingulum when compared with HC, and the SPD patients did not differ from HC or BPD individuals. In summary, the current study provides evidence of aberrant connectivity of the cingulum in BPD patients, but not SPD patients, compared with HC individuals. Consistent with prior work, overall results suggest potential involvement of cingulum in BPD symptomatology.

ACKNOWLEDGEMENTS

I want to thank all of my family, friends, colleagues, mentors, and supervisors who supported me throughout this project. Specifically, I wish to acknowledge my husband, Ivan Zinn, and my daughter, Aviva Zinn, for their constant love and patience. I would also like to thank Lauren Alloy, Erin Hazlett, Deborah Drabick, Tania Giovannetti, Michael McCloskey, Lauren Ellman, Mehmet Haznedar, and Kingwai Chu for their help, guidance, and support throughout the many stages of this project (i.e., which initially took the form of several F31 application submissions and is now a dissertation!).

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CHAPTER 1
INTRODUCTION

Borderline personality disorder (BPD) and schizotypal personality disorder (SPD) are two types of personality disorders characterized by inflexible and pervasive behavioral patterns that frequently lead to significant functional impairment. Although they are sometimes viewed as resulting from environmental factors, a large body of evidence suggests that BPD and SPD individuals exhibit domains of dysfunction associated with demonstrable neuroanatomical correlates (see Lis, Greenfield, Henry, Guile, & Dougherty, 2007, for review; Siever & Davis, 2004). Specifically, functional and anatomical studies most frequently implicate frontal and temporal brain abnormalities in both disorders (McCloskey, Phan, & Coccaro, 2005). Given this evidence, an important next step is to determine whether such abnormalities may be related to alterations in the connectivity of temporal and frontal lobe regions. This study expanded upon reports that frontal and/or temporal connectivity disturbances in BPD (Carrasco et al., 2012; Grant et al., 2007; New et al., 2013; Rüsch et al., 2007, 2010) and SPD (Gurrera et al., 2007; Nakamura et al., 2005) may reflect disruptions in the white matter tracts that link these brain regions. Specifically, the present study investigated one of the prominent white matter bundles connecting frontal and temporal cortex regions, the cingulum bundle (located in the cingulate gyrus), among BPD, SPD, and healthy control (HC) individuals.

To evaluate these white matter tracts, this study used diffusion tensor imaging (DTI). DTI is a unique magnetic resonance imaging (MRI) technique with several theoretical and methodological strengths. These strengths include the potential to offer direct *in vivo* evidence of abnormal connectivity in one of the major white matter fiber

tracts (standard MRI studies are unable to visualize fiber tracts) and ease of measurement in clinical populations due to its noninvasive nature. DTI examines the integrity of white matter tracts by measuring the directionality of water molecule movement, which then is used to infer the orientation and alignment of axonal tracts. One of the quantitative measurements of water molecule movement provided by DTI is called fractional anisotropy (FA; Taylor, Hsu, Krishnan, & MacFall, 2004). Decreased anisotropy frequently observed in some clinical populations (i.e., schizophrenia) is often thought to reflect anomalous myelination. Nonetheless, disrupted myelin is only one of many factors that influence anisotropy in white matter (Beaulieu, 2002). In this respect, deviations from parallel fiber measurement (i.e., fibers oriented in multiple directions) are also reflected as decreased FA. Ultimately, DTI measures can help us to make inferences about the organization and integrity of white matter, the course of axon bundles and, as a result, potential corresponding frontal-temporal connectivity deficits in BPD and SPD. To meet these goals, this project capitalized on a DTI dataset that included three groups of study participants: BPD, SPD, and HC.

Rationale for Comparing Borderline and Schizotypal Personality Disorder

There are several reasons for evaluating cingulum integrity in BPD and SPD. First, personality disorders are pervasive in the general population, very likely to co-occur with major mental disorders, and associated with serious impairment (Lenzenweger, Lane, Loranger, & Kessler, 2007). Second, little DTI research has been conducted to date in BPD (Carrasco et al., 2012; Grant et al., 2007; New et al., 2013; Rüsch et al., 2007; Rüsch et al., 2010) and SPD (Gurrera et al., 2007; Hazlett et al., 2011; 2012; Nakamura et al., 2005). Although considerable research has been conducted on

compromised frontal and temporal gray matter regions in BPD, this would be the first study to make a direct comparison of white matter tracts in two different personality disorders and the first to examine the integrity of different aspects of the cingulate (i.e., anterior, posterior) in both of the disorders. Because it remains unclear whether biological abnormalities are shared by or are specific to these personality disorders, it would be helpful to clarify the biological commonalities and distinctions between them. Knowledge of whether fronto-temporal white matter abnormalities are specific to one personality disorder, or whether the two groups differ from healthy controls in specific directions, would facilitate diagnostic and construct validity, consistent with standard criteria for classifying psychiatric illness, as well as provide a clearer picture of the pathophysiology and both clinical and neuropsychological symptom correlates of each disorder.

SPD is characterized by difficulties with language, paranoia, odd behavior, and magical thinking, as well as asocial tendencies. It was first introduced in the *DSM-III* and based on the clinical profiles of patients with "borderline schizophrenia" in the landmark Danish adoption studies of schizophrenia (Rosenthal, Wender, Kery, Welner, & Schulzinger, 1971). These studies and earlier formulations of the disorder suggested that relatives of individuals with schizophrenia may display deviant psychological functioning but not all signs of schizophrenia, providing evidence for a spectrum of schizophrenia-related disorders.

BPD, on the other hand, is characterized by affective instability and impulsive behavior, and it first appeared in *DSM-III* (Gunderson & Singer, 1975; Kernberg, 1977). Many of the earlier SPD studies included symptoms related to conceptions of BPD.

However, diagnostic overlap modestly decreased when the BPD criterion for paranoid ideation under stress was introduced in *DSM-III-R* (Spitzer, Endicott, & Gibbon, 1979). Nonetheless, comorbidity of BPD and SPD is not uncommon (Zanarini et al., 1998), which may be due to overlapping areas of neurobiological abnormalities and/or impaired domains of functioning (McGlashan et al., 2000). That is, research suggests the presence of cognitive/perceptual dysfunction in both BPD and SPD, including illusions/depersonalization/dissociation symptoms, which may lead to social functioning problems in both groups (Kavoussi & Siever, 1992; McGlashan, 1987). However, these disorders also have been shown to differ phenomenologically in some areas: emotion dysregulation and self-damaging acts characterize BPD individuals, whereas blunted affect and social isolation frequently characterize SPD (McGlashan, 1987).

Given these potentially overlapping and diverging neurobiological and phenotypic aspects of BPD and SPD, as well as the inherent complexity of both, this project offered a unique opportunity for clarifying commonalities and distinctions among and within groups. This project not only aimed to determine whether, compared with HCs, cingulum abnormalities are specific to one personality disorder, or whether SPD and BPD differ from each other, it also aimed to advance our limited understanding of the phenotypic aspects and individual differences within groups as well. This project aimed to compare all three groups on the basis of structural alterations in the cingulum and related clinical and cognitive factors.

Structural and Functional Abnormalities of the Frontal and Temporal Lobe in BPD

The frontal lobe has been identified as a key domain in potential BPD-related deficits in the fronto-temporal circuit because of its crucial role in cognitive control of

behavior, impulsivity, and emotion regulation processes. Specifically, studies have established the importance of the orbital frontal cortex (OFC) and anterior cingulate for the control of emotion and aggressive behavior (Davidson, Putnam, & Larson, 2000; Izquierdo, Suda, & Murray, 2005). In regards to temporal lobe regions, a substantive literature implicates the amygdala in emotional processes, including the perception, inhibition, regulation, and production of emotion (see Davidson & Irwin, 1999 for review). Several studies also have suggested the involvement of the hippocampus in BPD, a region shown to serve memory storage and retrieval functions, including emotion-laden memory (Scoville & Milner, 1957).

Although findings from morphologic investigations of frontal regions in BPD are inconsistent, there have been reports of reduced volume of the anterior and posterior cingulate gyrus (Hazlett et al., 2005; van Elst et al., 2003; Völlm et al., 2009), OFC (Chanen et al., 2008; van Elst et al., 2003; Völlm et al., 2009), and overall frontal lobe (Lyoo, Han, & Cho, 1998) in BPD. Structural MRI studies of temporal regions report hippocampal (Driessen et al., 2000; Irle, Lange, & Sachsse, 2005; Soloff et al., 2008, Zetzsche et al., 2007) and amygdala (Driessen et al., 2000; Rüsch et al., 2003; Schmahl et al., 2003; Soloff et al., 2008, van Elst et al., 2003) volume loss in BPD, although other studies have shown no significant structural differences between BPD individuals and controls in these regions (Chanen et al., 2008; New et al., 2007).

Stronger support for alterations in frontal and temporal regions in BPD is derived from functional studies of baseline activity and activation during specific emotion-related tasks. Resting positron emission tomography (PET) and single photon emission computed tomography (SPECT) studies have reported reduced frontal (OFC, anterior

cingulate) glucose metabolism (De la Fuente et al., 1997; Soloff, Meltzer, Greer, Constantine, & Kelly, 2000; Soloff et al., 2003), increased metabolic activity in anterior cingulate (Juengling et al., 2003), and decreased metabolic activity in OFC and anterior cingulate in response to serotonergic challenge in impulsive aggressive patients with BPD (New et al., 2004; Soloff et al., 2000). BPD functional imaging studies also have reported abnormal patterns of anterior cingulate, posterior cingulate, and OFC activity during the elicitation of negative memories (Beblo et al., 2006; Driessen et al., 2008; Schmahl et al., 2003; Schmahl, Vermette, Elzinga, & Bremner, 2004) and in response to emotional stimuli (Minzenberg et al., 2007; Schnell et al., 2007; Wingenfeld et al., 2009). In terms of temporal regions, BPD studies have reported abnormally heightened activation of amygdala to emotional stimuli (Donegan et al., 2003; Herpertz et al., 2001; Koenigsberg et al., 2009). Taken together, some morphologic and functional studies suggest that abnormal OFC, anterior cingulate, posterior cingulate, amygdala and/or hippocampal volume and/or activity are associated with BPD, although findings are somewhat mixed and dependent on the samples and methodologies used.

Structural and Functional Abnormalities of the Frontal and Temporal Lobes in SPD

The frontal lobe also has been viewed as a key domain in SPD-related deficits because it is implicated in studies of executive function, working memory, and attention impairment (Lees-Roitman, 2000; Weinberger et al., 2001). Temporal regions associated with SPD include amygdala and hippocampus because of their involvement in emotion and memory (see Davidson & Irwin, 1999 for review), areas where individuals with SPD reportedly experience difficulties. Superior temporal gyrus (STG) is also implicated

because of its role in language and auditory processing (Binder et al., 1994), domains of functioning where SPD individuals also manifest deficits.

Although volumetric reductions in frontal cortical regions have been reported in schizophrenia, several studies suggest these areas may be relatively preserved in SPD (Hazlett et al., 2008; Kawasaki et al., 2004; Suzuki et al., 2005). Haznedar and colleagues (2004) as well as others (Takahashi et al., 2004) reported no morphologic differences in cingulate gyrus in SPD but, using a larger sample size, this same group later found smaller anterior and posterior cingulate (Hazlett et al., 2008). Considerable work implicates SPD morphologic abnormalities in the temporal lobes, including reduced volume of STG (Buchsbaum et al., 1997b; Dickey et al., 1999; Goldstein et al., 2009; Hazlett et al., 2008; Kawasaki et al., 2004; Takahashi et al., 2006), middle and inferior temporal gyrus (Downhill et al., 2001), and Heschl's gyrus (Dickey et al., 2002b). Of note, Dickey and colleagues found decreased STG volume among male (2002b) but not female (2003) SPD individuals. Volume reductions in amygdala and/or hippocampal complex have been reported (Suzuki et al., 2005; Dickey et al., 2007), but not consistently observed (Dickey, McCarley, & Shenton, 2002a).

Functional imaging research using a variety of executive functioning, language, and memory tasks further implicate the frontal and temporal lobe in SPD. Among SPD individuals, a SPECT study reported greater activation in middle frontal gyrus during an executive functioning task (Buchsbaum et al., 1997a). Two PET studies measuring metabolic rate during verbal tasks reported abnormal activity patterns in SPD; specifically, greater metabolism in prefrontal regions (Buchsbaum et al., 2002) and posterior cingulate (Haznedar et al., 2004). Additional work suggests that SPD

individuals show increased activation in middle prefrontal regions but decreased activation in ventral prefrontal cortex during a visuo-spatial memory task (Koenigsberg et al., 2005). Functional studies of temporal regions have reported greater medial temporal cortex activation during a verbal learning task (Buchsbaum et al., 2002), as well as abnormal activation in the STG during auditory processing tasks (Dickey et al., 2008). Thus, morphologic and functional abnormalities suggest anterior and posterior cingulate, prefrontal (middle and frontal gyrus, ventral prefrontal), and temporal (STG, medial temporal) involvement in SPD.

Importance of Fronto-Temporal White Matter Connections

Taken as a whole, the described studies suggest that frontal and temporal lobe abnormalities are associated with BPD and SPD, although the regions implicated differ somewhat among studies depending on samples and methodologies employed. Nonetheless, these regions do not operate in isolation; they form integrated neural circuits through which these areas communicate and, together, enable proper functioning. To help determine whether these networks are associated with the difficulties experienced by individuals with BPD and/or SPD, a few recent DTI studies have borrowed a theory originally proposed by early schizophrenia researchers (Bleuler, 1911; Kraeplin, 1919; Wernicke, 1906): deficits associated with disrupted communication between frontal and temporal regions may reflect impairment in the white matter tracts connecting them. The present study extended this theory by directly comparing the integrity of one of the major fronto-temporal white matter pathways, the cingulum, in BPD and SPD.

The long association tracts connect cortical regions of different lobes within the same hemisphere and include three important fronto-temporal white matter bundles: the

cingulum bundle (located within the cingulate gyrus), the uncinate fasciculus, and the arcuate fasciculus. Importantly, studies have shown that maturation of the long association tracts continues through adolescence and, in some regions, into the twenties (Hasan et al., 2009; Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008). As such, changes in FA during this period of aging may reflect the developmental process of fiber myelination.

Neuroanatomy and Function of Cingulum

The cingulate gyrus, a region involved in the expression and recognition of emotion, sensory and motor functions, as well as memory and attention, has been implicated in BPD and SPD-related weaknesses. It contains the cingulum bundle, one of the three fronto-temporal white matter bundles described above, and forms an arch that begins at the rostral subcallosal area and follows the corpus callosum bilaterally on the sagittal plane (Goldman-Rakic, Selemon, & Schwartz, 1984; Haznedar et al., 2004; Pandya & Seltzer, 1982; Vogt, Rosene, & Pandya, 1979). The other end of the arch merges with the parahippocampal gyrus via the isthmus.

The anterior cingulate is divided into affect- and cognition-related sections. The ventral part constitutes the affect-related division and includes four Brodmann Areas (BAs 24, 25, 32, and 33; Bush, Luu, & Posner, 2000). It has extensive connections with the amygdala, periaqueductal gray matter, nucleus accumbens, hypothalamus, anterior insula, hippocampus, and OFC. In this respect, it enables decoding of external stimuli through the attribution of emotional content and is involved in the expression and regulation of inner emotional states. These two functions are crucial in social situations, as they help individuals understand emotional cues and then navigate the flow of social

interactions. Thus, given that BPD patients exhibit symptoms of both emotion dysregulation and interpersonal difficulties (Skodol et al., 2002), whereas SPD patients frequently show asociality (Siever & Davis, 2004), this study examined disruption in the white matter organization of the anterior cingulate, which may be associated with social and/or emotional difficulties in both groups.

The dorsal cognitive division of the anterior cingulate, on the other hand, is part of the attentional network and has extensive interconnections with lateral prefrontal cortex, parietal cortex, and premotor and supplementary motor areas (Bush et al., 2000). This cognitive-related region is thought to be involved in a number of functions, including modulation of attention/executive functions, motivation, working memory, and motor control. Given research suggesting BPD and SPD difficulties with cognitive functions subserved by the anterior cingulate cognitive division (e.g., cognitive inhibition on standard Stroop and emotional Stroop tasks: Arntz, Appels, & Sieswerda, 2000; Sieswerda, Arntz, Mertens, & Vertommen, 2007; and nonverbal/verbal working memory: Mitropoulou et al., 2005; Voglmaier et al., 2000), this study investigated white matter abnormalities in this region, which may be linked with the described BPD and SPD difficulties, respectively.

The posterior division of the cingulate consists of four BAs (23, 26, 29, 30 and 31) and is connected to the associative, temporal, mediotemporal, and orbitofrontal cortices and to the medial pulvinar. It is commonly implicated in visual inspection and navigation processes, and many aspects of memory, including visuospatial and verbal recall (Mesulam, Nobre, Kim, Parrish, & Gitelman, 2001; Nielsen, Balslev, & Hansen, 2005; Vann, Aggleton, & Maguire, 2009; Vogt, Finch, & Olson, 1992; Vogt & Laureys,

2005). Further, it is thought to be involved in episodic memory and retrieval of previously learned information regardless of its spatial content (Cabeza & Nyberg, 2000; Maguire & Mummery, 1999; Van Horn et al., 1998). Studies also indicate that the posterior cingulate is involved in self-referential processing (Ochsner et al., 2005; Vogt & Laureys, 2005), including involvement in the evaluation of positive and negative traits for self-relevance rather than social desirability (Fossati et al., 2003).

On this basis, the posterior cingulate appears to play an important role in social processing, an area of functioning where both SPD and BPD individuals manifest difficulties. Thus, posterior cingulate white matter abnormalities may be closely associated with their respective social challenges. In terms of cognitive functions subserved by posterior cingulate, neurocognitive studies suggest SPD weaknesses in attention and nonverbal learning/memory abilities (McClure et al., 2007; Mitropoulou et al., 2005) as well as verbal learning/memory abilities (Voglmaier, Seidman, Salisbury, & McCarley, 1997; Vogmaier et al., 2000), reflecting potential posterior cingulate dysfunction. In BPD, research also suggests difficulty with attention and nonverbal abilities (Judd & Ruff, 1993; see Ruocco, 2005 for review; Stevens, Burkhardt, Hautzinger, Schwarz, & Unckel, 2004), which may be tied to posterior cingulate abnormalities. Some BPD research reports verbal and nonverbal memory problems, other cognitive areas related to posterior cingulate functioning, but these findings are less consistent (Beblo et al., 2006; Kirkpatrick et al., 2007; Lenzenweger et al., 2004).

Previous DTI studies in BPD and SPD

To my knowledge, only three DTI studies have been conducted in SPD, all of which examined white matter fractional anisotropy in fronto-temporal regions. The first

reported lower FA in the uncinate fasciculus in SPD, but found no SPD-control group differences in the cingulate gyrus (Nakamura et al., 2005). However, Nakamura and colleagues did not differentiate between anterior and posterior cingulate white matter by analyzing FA values for these regions separately, which was an aim of the proposed study. SPD participants also showed a relationship between FA in cingulum bundle and both negative symptoms (reduced FA associated with more symptoms) and memory performance (reduced FA associated with more verbal memory errors, higher FA associated with better nonverbal memory performance). A second DTI study replicated the finding of lower FA in the UF of SPD individuals, and lower FA was associated with less extraversion and more neuroticism (Gurrera et al., 2007). And a third study (Hazlett et al., 2011) found reduced FA in the posterior cingulum (BAs 31 and 23) and increased FA in anterior regions (BA 25) in SPD. They also reported significant associations between lower cingulum FA and greater negative symptom severity. These findings are inconsistent with the lack of cingulum FA findings by Nakamura and investigators and, together with research showing functional heterogeneity in the cingulate (Vogt et al., 1992), suggest the need for future DTI work to differentiate between anterior and posterior cingulate, as the present study did.

Although one prior DTI study has examined the integrity of the cingulate in BPD and found reduced interhemispheric connectivity in the fibers that connect the dorsal aspects of the anterior cingulate (Rüsch et al., 2010), there have been no DTI investigations of the posterior cingulate white matter in BPD. That is, all of the DTI studies have assessed white matter integrity in and/or connected to general frontal (Carrasco et al., 2012; Grant et al., 2007; Rüsch et al., 2007) and temporal (New et al.,

2013) regions in BPD. Among this work, one study found decreased FA in inferior frontal regions in BPD (Grant et al., 2007), whereas another investigation reported reduced FA in longitudinal fasciculus, unicinate fasciculus, and occipitofrontal fasciculus of BPD adolescents but not BPD adults (New et al., 2013). Additionally, other work found no group differences from controls when examining inferior frontal white matter in women with BPD and attention-deficit/hyperactivity disorder (Rüsch et al., 2007).

The Current Study

This study is the first to examine FA in anterior and posterior cingulate separately in both BPD and SPD. Also, despite claims that BPD and SPD exhibit similar neurobiological abnormalities, scant research directly compares brain structure of these two groups. Given the complexity of these disorders and the many overlapping and diverging aspects both within and among personality disorder groups, a comparison of fronto-temporal white matter integrity similarities and differences could provide important information regarding the disturbances associated with these disorders and the role these white matter tracts may play in such dysfunctions. In this respect, the present study is also the first to make a direct comparison of these regions among BPD, SPD, and HC individuals, thus providing a clearer picture of the pathophysiology and clinical symptom correlates of each disorder.

Although the nature of FA alterations is still unclear, DTI offers a tool for investigating the integrity of white matter tracts implicated in the disconnection of specific brain regions. Thus, if FA deficits are detected, this study could improve knowledge of abnormal anatomical connectivity that may underlie these disorders. Results may drive future structural studies of regional and global white matter

abnormalities in personality disorders as well as postmortem studies examining microstructural differences (e.g., neuronal arborization, density, myelination) that may underlie FA deficits. Also, because this study ties FA alterations to clinical symptoms and cognitive performance, it also could drive future DTI research to examine cingulum integrity in more homogenous patient groups, such as those defined by a symptom profile, or to combine DTI with other functional methods (e.g., fMRI, transcranial magnetic stimulation) to further explore how fronto-temporal FA may be linked with neuronal function during specific tasks relevant to areas of dysfunction. Further, by comparing BPD with SPD, findings could advance knowledge of shared/distinct neuropathological and phenotypic aspects of personality disorders, potentially improving diagnostic validity and intervention efforts.

Last, this study may advance knowledge of developmental pathways. Research reports that maturation of the cingulum bundle continues through adolescence (Hasan et al., 2009; Lebel et al., 2008), suggesting it is most likely present at onset of BPD or SPD. Thus, findings could prompt longitudinal studies that examine whether FA deficits are driven by neurodevelopmental influences or reflect aspects of the disorder subsequent to onset. Results could fuel developmental hypotheses (e.g., alterations reflect neuroplastic adaptation to psychosocial impoverishment or neurohormonal response to traumatic events, halting development of myelination), potentially justifying intervention therapies during cingulum development.

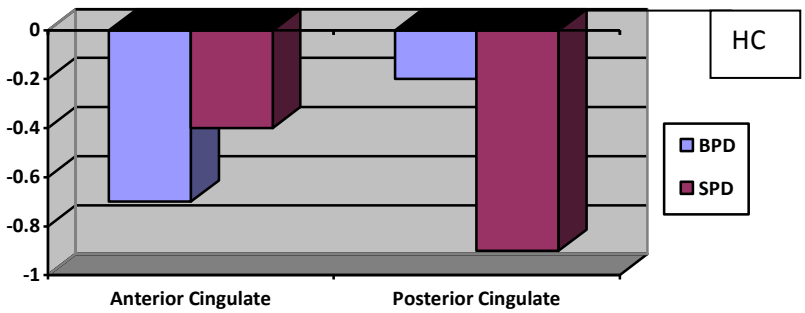

Figure 1. Hypothesized Results for Between-Group Fractional Anisotropy Analyses in Cingulate. This graph depicts our hypotheses that white matter abnormalities (low fractional anisotropy (FA)) in Schizotypal Personality Disorder (SPD) patients will be apparent in the posterior cingulate, whereas white matter abnormalities in Borderline Personality Disorder (BPD) patients will be apparent in anterior cingulate.

AIM 1: Examination of Group Differences in Anterior and Posterior Cingulate

The first major aim of this project was to confirm the model depicted in Figure 1.

Hypothesis 1: The first hypothesis was that a spectrum pattern would be observed in anterior cingulate white matter fractional anisotropy with HC>SPD>BPD. Lower FA in the anterior white matter region in BPD would be consistent with the hypothesis that connectivity of the anterior cingulate to other brain regions is altered in BPD. Although I expected anterior cingulate white matter integrity to be somewhat disrupted in SPD individuals, alterations were predicted to be more apparent in BPD given more consistent findings of anterior cingulate abnormalities in BPD as compared with SPD (Hazlett et al., 2005). Additionally, I did not have specific hypotheses regarding group white matter FA differences in anterior cingulate subdivisions; however, on an exploratory basis, I analyzed whether BPD individuals demonstrate lower white matter FA in the affective division of the anterior cingulate, as compared with HC and SPD, and whether SPD

patients show lower FA in the cognitive division of the anterior cingulate, as compared with HC and BPD (Bush et al., 2000). However, I hypothesized a different spectrum pattern would emerge in posterior cingulate white matter FA with HC>BPD>SPD. The finding of lower FA in the posterior region in SPD would be consistent with the hypothesis that connectivity of the posterior cingulate to other regions is altered in SPD. It is also in line with a recent finding of reduced FA in posterior cingulate white matter in SPD (Hazlett et al., 2011).

AIM 2: Examination of Associations between the Cingulum and Clinical/Cognitive Measures.

Given findings that reduced FA in the cingulate correlated with higher symptom ratings and lower memory function in SPD (Nakamura et al., 2005), I examined correlations between anterior/posterior white matter fractional anisotropy and measures of clinical and cognitive functioning. Of note, although collection of the cognitive data took place during the same time period that the primary imaging studies took place, only a small subset of the participants underwent this testing (BPD n = 7; SPD n = 26; HC n = 16; Table 3).

Hypothesis 2: These analyses were exploratory, but I predicted the following results would be the same in BPD and SPD: given the suggested role of anterior cingulate in social, emotional, and cognitive functioning, and considerable evidence documenting difficulties in these areas in both BPD and SPD, I expected reduced FA in anterior cingulate white matter would be associated with higher clinical symptom severity in both diagnostic groups. However, I predicted the following results would differentiate BPD and SPD: in anterior cingulate, because of its suggested role in emotion regulation (rostral-ventral affective division), a primary area of impairment in BPD (Arntz, et al.,

2000; Leyton et al., 2001; Linehan et al., 1993; Rentrop et al., 2008; Sieswerda et al., 2007), I predicted reduced white matter FA would be associated with higher emotion-related symptomatology as well as the Affective Intensity Measure (AIM; Larsen & Diener, 1987) and the Affective Lability Scale (ALS; Harvey, Greenberg, & Serper, 1989) scores in BPD. Given research showing the posterior cingulate's involvement in verbal and nonverbal memory, and evidence of SPD verbal difficulties on the California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 1987) and working memory deficits on spatial working memory (SWM) tasks in SPD that are not consistently reported in BPD (Mitropoulou et al., 2005; Voglmaier et al., 2000), I expected that lower CVLT and SWM scores (collected in a small subset of the participants) would correlate with reduced FA in posterior cingulate white matter in this diagnostic group.

CHAPTER 2
EXPERIMENT – METHODS

Data Set Information

Data for the present study were collected as part of three NIMH R01 fMRI grants that also collected supplementary DTI data which were analyzed for the current project. These grants are entitled "Neural substrates of emotion in borderline personality disorder" (primarily from PI: Erin A. Hazlett, Ph.D.; R01 MH073911-02), "Working Memory" (PI: Harold W. Koenigsberg, M.D.; R01 MH069947-01), and "fMRI Study of Emotional Dysregulation in Borderline Personality Disorder" (PI: Harold W. Koenigsberg, M.D.; R01MHO77813-01), all of which took place at Mount Sinai School of Medicine. DTI data were not explicitly part of the specific aims for any of these studies, but were collected in the entire sample. Drs. Hazlett and Koenigsberg gave me permission to use these de-identified data for this study. In addition, I was also granted approval by the Temple University Institutional Review Board to use these de-identified data for this study.

Participants

Overall, 96 participants were included in the current study. Participants included 36 HC, 28 BPD individuals, and 32 SPD individuals (Table 1). The groups did not differ significantly on age, sex, or highest educational degree earned. Primary demographics were as follows: BPD—female: 57%, age: M = 31.1 (SD=9.5); SPD—female: 38%, age: M = 34.9 (SD = 10.0); HC—female: 50%, age: M = 32.3 (SD = 9.1).

Table 1. Demographics of Study Sample

Variable	BPD(n=28)	SPD(n=32)	HC(n=36)	Test Statistic
Age (years)	31.1 (9.5)	34.9 (10.0)	32.2 (9.1)	F(2,93)=1.27, p=.30
range	18-51	21-55	22-56	
Education	4.8(2.7)	4.4(1.9)	5.4(2.7)	F(2,81)=1.44, p=.24
Gender				
Male	12(43%)	20(63%)	18(50%)	$\chi 2(2)=2.41$, $p=.30$
Female	16(57%)	12(37%)	18(50%)	
Ethnicity	BPD(n=24)	SPD(n=30)	HC(n=27)	$\chi 2(6)=9.9$, $p=.13$
Caucasian	15(63%)	13(43%)	18(67%)	
African American	5(31%)	13(43%)	3(11%)	
Asian	4(17%)	3(10%)	4(15%)	
Other	0	1(3%)	2(7%)	

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. *$p < .05$ (2-tailed).

Interview and Self-Report Measures

Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I; First et al., 1996). The SCID is a semi-structured interview that has been widely used in research settings to make DSM-IV Axis I diagnoses. It is divided into separate modules corresponding to categories of diagnoses. Research reports adequate inter-rater reliability, as kappa values have been reported to be between 0.70 and 1.00 (First et al., 1996; Lobbestael, Leurgans, & Arntz, 2011; Zanarini et al., 2000), and inter-rater reliability for the current study was between 0.75 and 0.80 for the different diagnoses.

Structured Interview for DSM-IV Personality Disorders (SIDP; Pfohl et al., 1997). The SIDP is a semi-structured interview used to assess the diagnostic criteria for the 10 DSM-IV personality disorders. The questions are organized by themes (relationships, emotions, interests) and each criterion is rated on a scale from 0 to 3. It has been shown to have good reliability and validity (Jane, Pagan, Turkheimer, Fiedler, & Oltmanns, 2006). For the present study, intra-class correlations (ICC) were 0.80 for BPD diagnosis, and .73 for SPD diagnosis.

Affective Lability Scale (ALS; Harvey, Greenberg, & Serper, 1989). The ALS is a self-report measure of lability of affect. It assesses the participant's perceptions of their ability to change from what they consider to be their normal mood to anger, depression, elation, and anxiety. The scale also measures the extent to which they perceive themselves to shift between the states of depression and elation and between the states of depression and anxiety. Each of the 54 items is rated on a 4-point scale according to how "true" each statement is for them, ranging from "very uncharacteristic" to "very characteristic" of themselves. The total ALS score is the mean of the six individual affect shift scales. It demonstrates a high level of internal consistency ranging from 0.73 to 0.89 and adequate test-retest reliability (Harvey, Greenberg, & Serper, 1989). Internal consistency for the current study was 0.98.

Affective Intensity Measure (AIM; Larsen & Diener, 1987). The AIM is a 40-item self-report scale that measures affect intensity to a given level of emotion-provoking stimulation. The participant rates each item on a 6-point scale ranging from "never" to "always". The total AIM score is the mean of the items. This measure demonstrates internal consistency ranging from 0.84 to 0.94, and test-retest reliability of 0.75 to 0.81

(Larsen, Diener, & Emmons, 1986; Flett & Hewitt, 1995). In the present study, internal consistency was 0.83.

Cognitive Measures

California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 1987). The CVLT is a measure of verbal list-learning abilities; it involves five presentations of a list of 16 words (four words from each of four semantic categories), with recall after each presentation. Dependent variables include performance on trials 1 through 5, short delayed free recall, short delay cued recall, long delay free recall, and long delay cued recall. Research reports adequate internal consistency reliability and test-retest stability (Delis et al., 1987).

Spatial Working Memory Task/Cambridge Neuropsychological Test Automated Battery (Luciana et al., 2002). Spatial Working Memory assessment is a task from the Cambridge Neuropsychological Test Automated Battery. Blue tokens are "hidden" behind colored squares on the screen and the participant is asked to locate the tokens using the process of elimination until they have found enough tokens to fill up an empty column on the side of the screen. Only one token is hidden on each trial, and a token is never hidden more than once in the same location. The outcome measures are the number of errors made and a strategy score which measures the ability to adopt a consistent search sequence. SWM demonstrates adequate test-retest reliability (Robbins et al., 1994; 1998).

Image Acquisition and Processing

MRI acquisition occurred on a Siemens Allegra 3T head-dedicated MRI system to acquire axial structural and diffusion tensor images 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 $b = 1250$ x/mm^2 were used (TR = 4100 ms, TE = 80 ms, FOV = 21 cm, matrix = 128 x 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-colinear 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 diffusion tensor was then obtained by solving the 13 simultaneous signal equations relating the measured signal intensity to the diffusion tensor (Basser et al., 1994b; Papadakis et al., 1999). This resulted in a tensor for every voxel (1.6 x 1.6 x 3 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 x 256, 208 slices with thickness = 0.82 mm) was also obtained.

FA was used to determine the degree of diffusion anisotropy in each voxel. FA is a measure of the degree to which the diffusivity is biased along the fiber axis as opposed to perpendicular to it. It is a scalar quantity that is invariant under rotation and translation. 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 (Figure 2). 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.

Cingulate Tracing on MRI

The left and right anterior and posterior cingulate were traced on axial MR images. First, I outlined the cingulate gyrus on each subject's MP-RAGE structural MRI. I also outlined the entire cingulate gyrus 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). Tracing began ventrally with the plane showing the appearance of the cingulate sulcus in place of the gyrus rectus and ended dorsally with the plane showing the disappearance of the corpus callosum (Haznedar et al., 2000). Outlining of the posterior cingulate started at the axial plane on which the splenium of the corpus callosum could be visualized. Tracing was carried out dorsally, and at the axial plane where the corpus callosum disappears and the anterior and posterior cingulate merge, the x-y coordinates of the merging point were identified. These coordinates were then designated as the margins of the anterior cingulate and the posterior cingulate on higher axial planes. Inevitably, defining the posterior cingulate with the deepest sulcus in the

parietal and the occipital lobes excludes posterior cingulate Brodmann areas 30 and 31; however, this approach has the advantage of excluding medial-parietal and medial-occipital cortex areas such as the precuneus. 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. However, Brodmann's areas (Brodmann, 1909) cannot be reliably identified on MRI. As such, to determine mean FA for each region of the cingulate, I divided the anterior cingulate into six equal axial segments and the posterior cingulate into two segments on the basis of proportions derived from the Talairach-Tournoux atlas (Talairach & Tournoux, 1988). Table 2 depicts the approximate Talairach coordinates, DTI brain atlas pages (Mori, Wakana, Nagae-Poetscher, & van Zijl, 2005), and Brodmann areas including the segments. With this approach, I was able 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 (Figure 2).

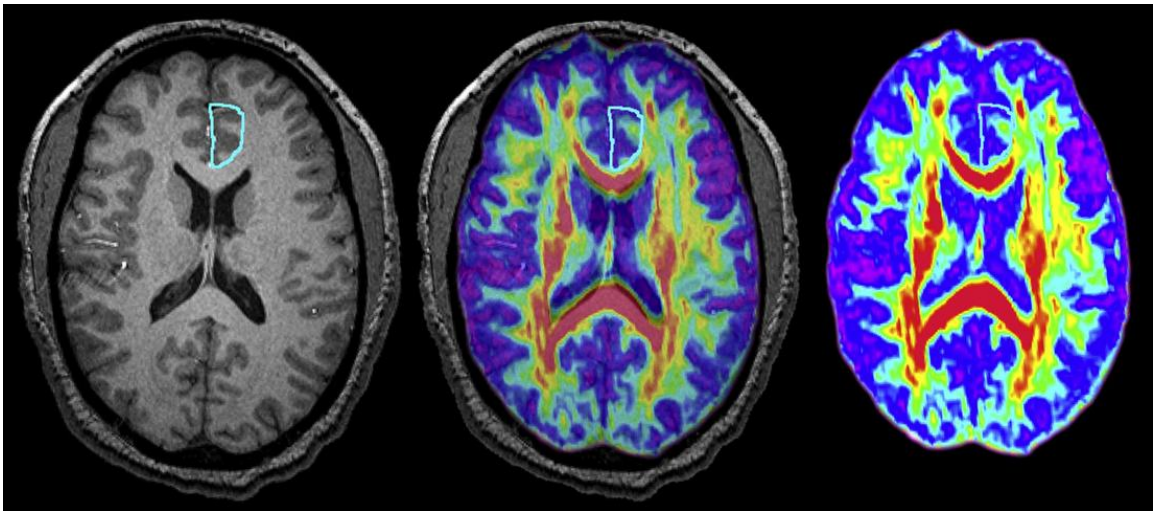

Figure 2. Depiction of Co-registration of Anisotropy Map with the T1-weighted Image. Left: axial MRI image with the left anterior cingulate gyrus traced. Center: fused image depicting the co-registration of the anisotropy map with the T1-weighted image. Right: FA map obtained with diffusion tensor acquisition. The color scale indicates FA values, as the highest FA values are seen in the corpus callosum and intermediate values are seen in the cingulum bundle.

Table 2. Approximate Correspondence of Anterior and Posterior Cingulate Segments to Published Co-ordinates and Brodmann Areas

Segment	Talairach coordinates (Talairach & Tournoux, 1988)	Pages in Mori et al. (2005)	Brodmann areas (Brodmann, 1909; Vogt et al., 1995)
ACG 1	-4 to +1	pp. 66-74	25
ACG 2	+1 to +8	pp. 74-78	24, 32
ACG 3	+8 to +12	pp. 78-84	24, 32
ACG 4	+12 to +20	pp. 84-92	24, 24', 33
ACG 5	+20 to +24	pp. 92-98	24, 24', 33
ACG 6	+24 to +28	pp. 98-102	24, 24'
PCG 1	+12 to +20	pp. 80-90	26, 29, 30, some 23
PCG 2	+20 to +28	pp. 90-102	23

Note. ACG = anterior cingulate gyrus. PCG = posterior cingulate gyrus.

Procedure

All participants were unmedicated at the time of their MRI scan (>6 weeks). Participants with a history of schizophrenia, psychotic disorder, bipolar (type I) affective disorder, or with current major depressive disorder (MDD) (episode occurring within 2 months of the scan) were excluded. Healthy control participants had no current Axis I diagnosis and no current Axis I disorder in any first-degree family member. However, 11 of the BPD patients and three of the SPD patients had past history of Major Depressive Disorder. Also, in terms of BPD patients, 21% had co-morbid paranoid personality disorder, 7% had avoidant personality disorder, 29% had obsessive-compulsive personality disorder, 25% had narcissistic personality disorder, 7% had histrionic personality disorder, and 7% had antisocial personality disorder. Of the SPD patients, 38% had paranoid personality disorder, 34% had avoidant personality disorder, 31% had obsessive-compulsive personality disorder, 3% had narcissistic personality disorder, 13% had schizoid personality disorder, 3% had antisocial personality disorder, and 9% had dependent personality disorder. Participants with a severe medical/neurological illness or head injury were also excluded. The majority of participants were recruited via advertisements in local newpapers and online social network sites (e.g., Craig's list). Approximately 10% of the SPD and BPD participants were recruited by referral from psychiatric clinics at Mount Sinai School of Medicine. All participants provided written informed consent in accordance with the Mount Sinai School of Medicine Institutional Review Board guidelines.

Clinical Assessment

All eligible participants (including healthy controls) received a full diagnostic structured interview that included the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I; First, Spitzer, Gibbon, & Williams, 1996) and the Structured Interview for DSM-IV Personality Disorders (SIDP; Pfohl, Blum, & Zimmerman, 1997). Weekly consensus and diagnostic meetings were led by a psychologist. All patient interviews were conducted by doctoral level psychologists who were specifically trained in the assessment of Axis II disorders. In Hazlett's laboratory, the intraclass correlation for BPD diagnosis was 0.80 and for SPD it was 0.73. All patients met DSM-IV criteria for either BPD or SPD. For each patient, 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. 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. To quantify the level of clinical symptom severity, individual symptom ratings were summed for each diagnostic criterion.

Cognitive Assessment

Neuropsychological measures (i.e. verbal and nonverbal memory tasks) were not a component of the study initially and thus were administered only to a subset of the original sample. As a result, these analyses were conducted on an exploratory basis.

Data Analytic Plan

First, I assessed group differences in age, education, and sex using Student *t*- tests and chi-square, as appropriate. The cingulate gyrus volume can vary substantially among participants, so I corrected for these variations by dividing the volume of each participant's anterior cingulate and posterior cingulate by his or her intracranial volume as determined by outlining the brain on each T1-weighted slice. Volumes are thus expressed as a fraction of brain volume. To test the hypothesized group differences in cingulum, I used a mixed-factorial design MANOVA with diagnostic group as the categorical predictor (HC vs. SPD vs. BPD). Given that no differences in age, sex or education were detected, I did not include them as covariates. For the cingulum analyses, repeated measures included hemisphere (left, right), segment (1-8 from anterior to posterior, Figure 3) and tissue type (gray, white). All significant effects were confirmed with the Wilks multivariate test for repeated measures. Fisher's LSD tests were then conducted to follow-up significant interactions among diagnostic group and hemisphere, segment and/or tissue type. Statistical significance for all volume and FA comparisons was set at $p < 0.05$. I then used Pearson's correlation coefficients (Bonferroni corrected) to examine associations between FA and clinical/cognitive variables.

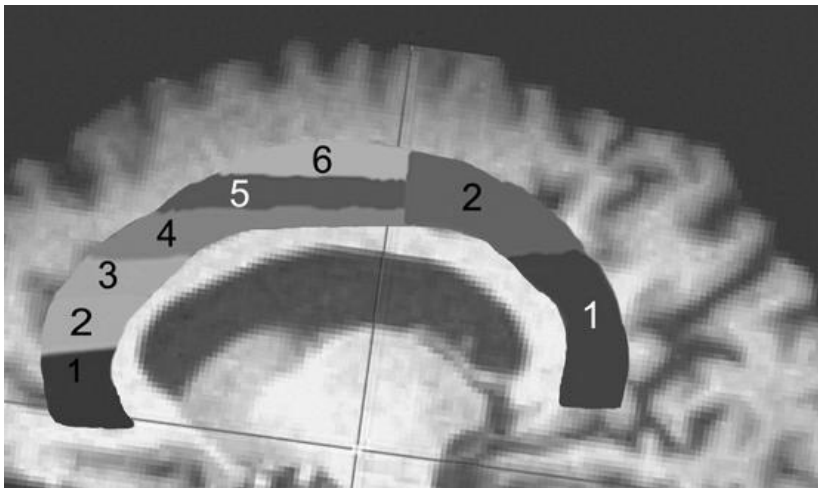

Figure 3. Sagittal Depiction of Cingulate Divided into Axial Segments. Anterior segments one through six constitute anterior cingulate; posterior segments one and two make up posterior cingulate.

CHAPTER 3
EXPERIMENT – RESULTS

All data were analyzed for normality using the Kolmogorov-Smirnov test of normality. Overall results from these tests indicated that there was no need to transform the data.

Preliminary Analyses

The demographic information for the total sample is included in Table 1. Overall, there was no difference in age, education, and gender between BPD and HC, SPD and HC, and BPD and SPD ($p > .05$), respectively. Means and standard deviations of the main clinical and cognitive variables of interest are presented in Table 3 for the overall sample.

Table 3. Means and Standard Deviations of Primary Clinical and Cognitive Measures

Variable	BPD		SPD		HC		*F*
	M (SD)	*n*	*M (SD)*	*n*	*M (SD)*	*n*	
AIM	3.82 (0.71)	27	3.52 (0.52)	31	3.32 (0.53)	31	5.35, $p = .01$[a]
ALS	1.51 (0.60)	28	1.05 (0.64)	31	0.39 (0.32)	33	33.93, $p = 0$[a,b,c]
SWM							
BE	19.33 (11.24)	3	41.0 (23.77)	13	24.5 (19.75)	6	1.92, $p = .17$
SS	27.33 (6.11)	3	34.46 (5.80)	13	34 (4.34)	6	2.11, $p = .15$
CVLT							
T1	6.86 (2.04)	7	7.04 (1.66)	26	9.31 (2.77)	16	6.35, $p = .004$[a,b]
T2	10.29 (1.70)	7	10.00 (2.47)	26	11.63 (2.42)	16	2.40, $p = .10$
T3	12.00 (2.94)	7	10.96 (2.34)	26	12.94 (1.95)	16	3.66, $p = .03$[b]
T4	13.00 (1.15)	7	11.62 (2.64)	26	13.63 (1.82)	16	4.20, $p = .02$[b]
T5	13.43 (1.27)	7	12.31 (2.65)	26	13.31 (1.96)	16	1.26, $p = .29$
B	6.00 (2.24)	7	5.85 (2.31)	26	7.06 (2.67)	16	1.30, $p = .28$
SDFR	12.86 (1.21)	7	10.69 (2.88)	26	12.94 (2.11)	16	4.89, $p = .01$[b]
SDCR	13.29 (1.60)	7	11.23 (2.72)	26	13.38 (2.00)	16	4.85, $p = .01$[b]
LDFR	13.14 (1.57)	7	11.04 (3.18)	26	13.25 (2.18)	16	3.94, $p = .03$
LDCR	13.71 (1.50)	7	11.81 (2.06)	16	13.25 (1.95)	16	4.13, $p = .02$

Note. BPD = Borderline Personality participants. SPD = Schizotypal Personality Disorder participants. HC = Healthy Control participants. AIM = Affective Intensity Measure. ALS = Affective Lability Scale. SWM = Spatial Working Memory task. BE = Between Search Error Score. SS = Strategy Score. CVLT = California Verbal Learning Test. T1 = Trial 1 Learning. T2 = Trial 2 Learning. T3 = Trial 3 Learning. T4 = Trial 4 Learning. T5 = Trial 5 Learning. B = List B Learning. SDFR = Short Delay Free Recall. SDCR = Short Delay Cued Recall. LDFR = Long Delay Free Recall. LDCR = Long Delay Cued Recall. [a] BPD differ from HC, $p < .05$ (2-tailed). [b] SPD differ from HC, $p < .02$ (2-tailed). [c] BPD differ from SPD, $p < .01$ (2-tailed).

Volume

The whole brain volume did not differ significantly among the groups (one way ANOVA, F (2,93) = 1.4, $p > .2$, $\eta\rho^2 = .03$ (means: HC 1591085±162321.1; BPD 1538409±114947.0; SPD 1545330±124819.1). Further analyses examining cingulate volume showed that there was a significant interaction of group and tissue type affecting volume (MANOVA (Diagnosis x Tissue type) F (2, 93) = 4.23, $p < .02$, $\eta\rho^2 = .08$, Wilks (Figure 4)). *Post-hoc* Fisher's LSD tests revealed that SPD patients had significantly smaller relative white matter volume compared with healthy controls ($p < .01$, $d = 1.0$), and BPD patients showed significantly smaller relative white matter volume compared with healthy controls at a trend level with a medium effect size ($p = .05$, $d = .6$). However, the patient groups did not differ from each other on relative gray and white matter volume, and none of the other interactions with diagnostic group were significant (Diagnosis x Hemisphere, Diagnosis x Segment, Diagnosis x Segment x Hemisphere, Diagnosis x Tissue type x Hemisphere, Diagnosis x Tissue type x Segment, and Diagnosis x Tissue type x Segment x Hemisphere, ($p > 0.20$)).

Fractional Anisotropy – Hypothesis 1

Given the significant between-group difference in volume, I conducted a MANCOVA to determine differences in FA among the three diagnostic groups, using overall cingulate volume as the covariate. Overall, there was no main effect of group ($p > .8$), but a Diagnosis x Segment x Tissue type interaction effect on FA was significant at a trend level (MANCOVA (Diagnosis x Segment x Tissue type), F (14, 172) = 1.65, $p = .07$, $\eta\rho^2 = .02$, Wilks). The effect showed that the BPD patients had lower FA in a segment of the posterior cingulate white matter (segment 2 of posterior cingulate; BA 23;

Fisher's LSD, $p = .05$, $d = 1.0$). Additionally, none of the other interactions reached significance (Diagnosis x Hemisphere, Diagnosis x Segment, Diagnosis x Tissue type, Diagnosis x Segment x Hemisphere, Diagnosis x Tissue type x Hemisphere, Diagnosis x Tissue type x Segment x Hemisphere, p's > .10). However, given the large effect size detected in BPD patients as well as my specific a priori hypotheses for each patient group compared with controls, which were based on our group's prior findings using smaller samples and 1.5T MRI (Haznedar et al., 2004), I conducted two-group analyses for my specific hypotheses. Results revealed a Diagnosis x Segment x Tissue type effect on FA, $F (7, 55) = 2.36$, $p < .04$, Wilks. Specifically, compared with healthy controls, BPD patients displayed significantly lower FA in a segment of the posterior cingulate white matter (segment 2 of posterior cingulate; BA 23; Fisher's LSD, $p < .04$, $d = 1.0$; Figure 5) and lower FA in a segment of the anterior cingulate white matter (segment 4 of anterior cingulate; BA's 24, 24', 33; Fisher's LSD, $p = .05$, $d = .8$). Of note, none of the other interactions were significant (Diagnosis x Hemisphere, Diagnosis x Segment, Diagnosis x Tissue type, Diagnosis x Segment x Hemisphere, Diagnosis x Tissue type x Hemisphere, Diagnosis x Tissue type x Segment x Hemisphere, p's > .2). Further, a significant difference in the FA of cingulate gray and/or white matter was not detected between SPD patients and healthy controls, nor was a difference detected between BPD patients and SPD patients, (p's > .05).

Clinical Symptomatology and Correlations – Hypothesis 2

In order to determine whether volume should be used as a covariate in correlational analyses, I initially conducted Pearson's correlations between FA (in the regions where significant differences were detected from healthy controls) and volume

(in the regions where significant differences were detected). Results indicated that FA in segment 4 of the anterior cingulate was associated with volume of the same region in HC (r = .44, n=36, p = .007), such that, among HC, the higher the FA in this region, the greater the volume. However, this relationship did not differ between groups (HC vs. BPD, Fisher's Z test = .36, p = .70; HC vs. SPD, Fisher's Z test = .98, p = .33). No other significant associations between FA and volume in posterior and anterior cingulate were detected, p's > .10. Thus, because a significant relationship was not found in the patient groups, volume was not used a covariate when examining relations between FA and clinical/cognitive variables.

As such, given previous work showing an association between negative symptoms and FA measures in the cingulum bundle of SPD patients (Nakamura et al., 2005), Pearson's correlations were then calculated for patient groups and HC's to examine the association between clinical symptomatology and FA in brain regions where patient groups showed significant FA differences from healthy controls. Unexpectedly, we found that higher FA in segment 2 of posterior cingulate (BA 23) in BPD patients was associated with greater BPD symptom severity (r = .39, n = 28, p = .04) as well as higher levels of transient, stress-related paranoid ideation or severe dissociative symptoms (r = .39, n = 28, p = .04). In SPD patients, higher FA in segment 4 of anterior cingulate (BA's 24, 24', 33) was associated with increased suspiciousness or paranoid ideation (r = .40, n = 31, p = .03) and more inappropriate/constricted affect (r = .36, n = 31, p = .04). However, upon applying the Bonferroni correction to adjust for multiple comparisons, none of the above-mentioned correlations remained statistically significant. In addition, none of the other correlations with BPD clinical symptomatology (i.e., efforts to avoid

abandonment, unstable interpersonal relationships, identity disturbance, impulsivity, suicidal behavior, affective instability, chronic feelings of emptiness, inappropriate anger) and self-report responses on the AIM and ALS reached significance (p's > .10), nor did any of the other correlations with SPD clinical symptomatology (i.e., SPD symptom severity, ideas of reference, odd beliefs/magical thinking, unusual perceptions, odd thinking and speech, odd behavior, lack of close friends, excessive social anxiety) and self-report responses on the AIM and ALS, p's > .10.

Next, exploratory neuropsychological correlates for the BPD and SPD groups were conducted in the brain regions where significant FA differences were detected due to prior work reporting significant associations between verbal memory performance and FA in anterior brain regions (Grant et al., 2007). In the BPD, SPD and HC groups, no significant associations were found between FA variables and performances on a spatial working memory task, p's > 0.05. Nonetheless, a small subset of the study sample was administered the CVLT. Results showed that, among the BPD patients, lower FA in segment 4 of anterior cingulate was associated with stronger performance on the second trial of the task (BPD: r = -.91, p = .004, n = 7; SPD: r = .14, p = ns; HC: r = -.01, p = ns; BPD vs. SPD, Fisher's Z test = -3.1, p = .002 ; BPD vs. HC, Fisher's Z test = -2.7, p = .008), as well as the short delay cued recall trial (BPD: r = -.92, p = .004, n = 7; SPD: r = .38, p = ns; HC: r = .15, p = ns; BPD vs. SPD, Fisher's Z test = -3.7, p = .0002; BPD vs. HC, Fisher's Z test = -3.0, p = .002), all of which survived the Bonferroni correction of .004. Of note, all of the BPD participants performed within normal limits for age and education on this task. In addition, none of the associations between FA variables and other trials of the CVLT reached statistical significance and survived Bonferroni

correction in the BPD group (p's > .03), and none of the associations between FA variables and verbal memory performance in SPD patients reached statistical significance, $p's$ > .06.

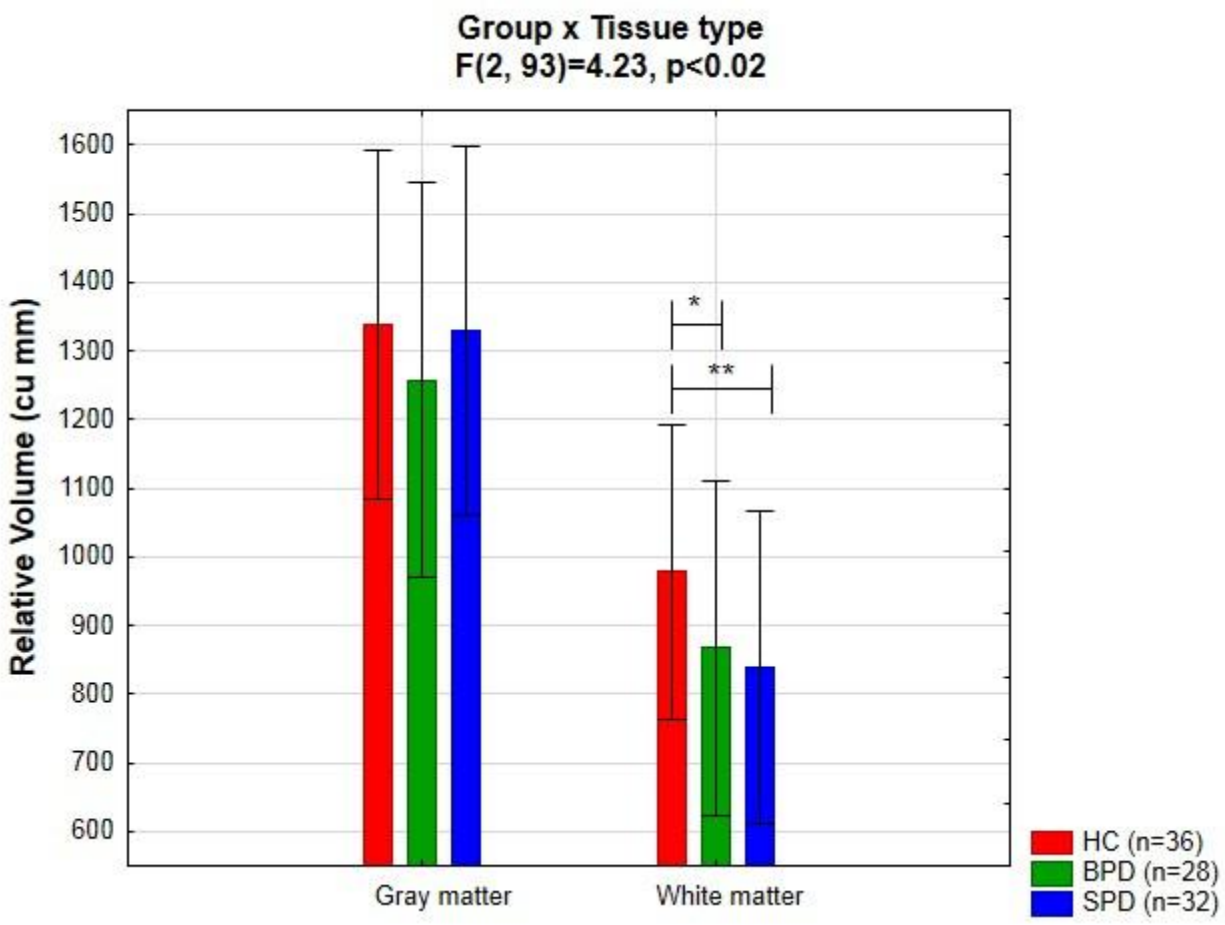

Figure 4. Relative volumes of overall cingulate gray and white matter (averaged over hemisphere and expressed in cubic millimeters). Volumes are expressed as a fraction of the whole brain volumes. Vertical bars indicate 95% confidence intervals. *p = .05; **p < .05 (2-tailed).

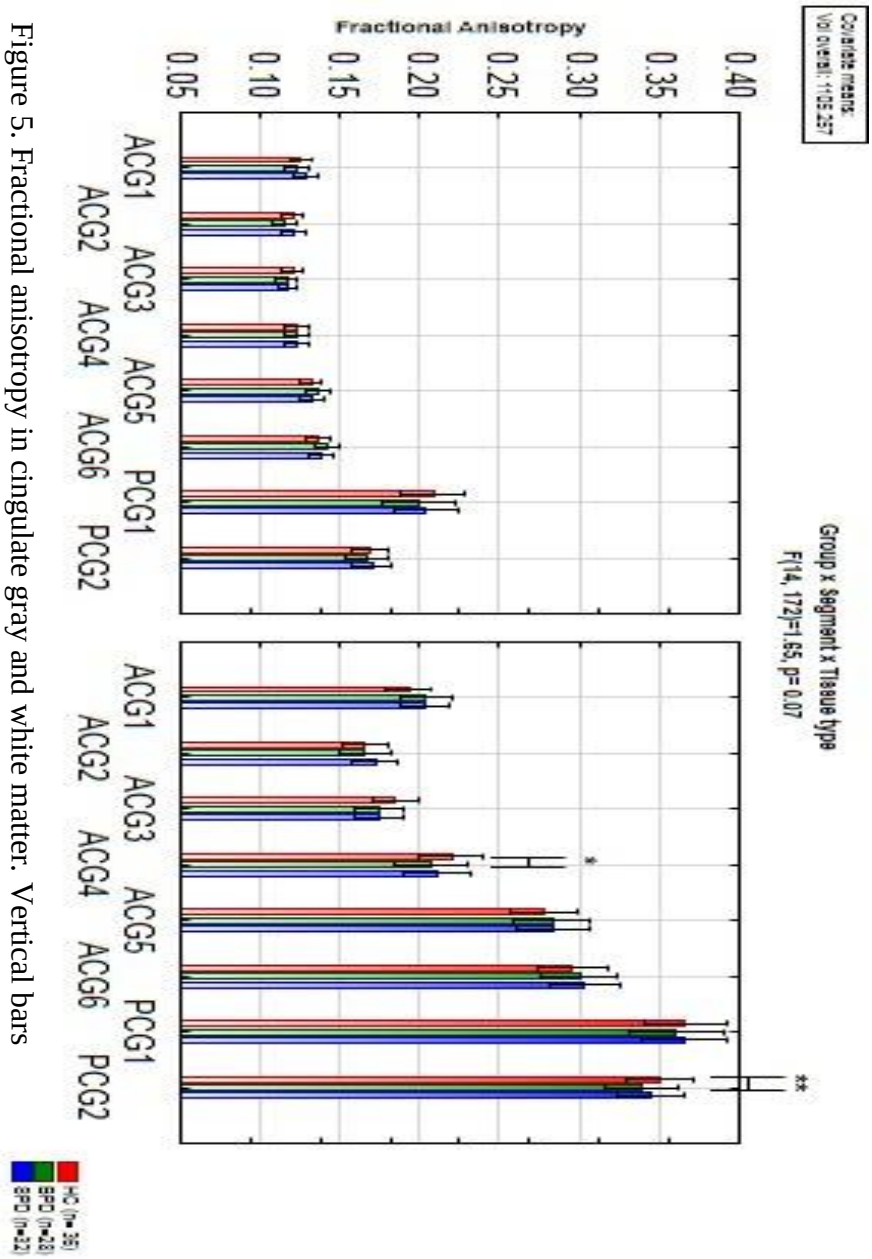

Figure 5. Fractional anisotropy in cingulate gray and white matter. Vertical bars indicate 95% confidence intervals. Note. *p = .05; **p < .05 (2-tailed).

CHAPTER 4
DISCUSSION

Although many neuroimaging studies have been published on individuals with BPD and SPD, respectively, very few have directly compared these psychiatric groups with one another. As such, much remains to be learned about their biological and phenomenological commonalities and distinctions. The current study aimed to address this issue by directly assessing cingulum integrity in BPD and SPD, given the preponderance of studies implicating this brain region in both disorders. The results indicated that, compared with healthy controls, BPD patients exhibited significantly lower FA in posterior cingulate white matter and marginally lower FA in anterior cingulate white matter. Although SPD patients displayed lower cingulate white matter FA relative to healthy controls, the results did not reach statistical significance.

To start, the FA findings from the current study are partially consistent with the primary hypotheses proposed. Specifically, results are congruent with our hypothesis that BPD patients would exhibit decreased FA in posterior cingulate white matter as compared with healthy controls. However, unexpectedly, SPD patients did not show decreased FA in posterior cingulate white matter compared with HC or BPD patients (which will be addressed below). With regard to anterior cingulate findings, a spectrum pattern emerged, such that BPD patients displayed decreased FA in a dorsal segment of the anterior cingulate (albeit results trended towards a significant difference from HC in this area) and SPD patients were intermediate between BPD patients and HC (albeit not significantly lower than HC), which was congruent with the study's primary hypothesis.

In this respect, the present findings extend the work of several DTI studies that report on reduced white matter integrity in frontal regions and fiber tracts that connect frontal regions in adults with BPD (i.e., Carrasco et al., 2012; Grant et al., 2007; Rüsch et al., 2007, 2010) and temporal regions in adolescents with BPD (New et al., 2013). That is, the current study not only examined white matter integrity of a specific frontal region that connects with many of the areas implicated in these prior studies, it also compared a sample of BPD patients without comorbid personality disorders with both healthy and psychiatric controls, thus providing greater specificity in examining potential biological markers that may set these patients apart from individuals with other personality disorders. Additionally, given the possibility that white matter volumetric abnormalities may be contributing to findings of reduced white matter FA in the areas examined, we also included volumetric analyses to help determine if and to what extent volume may be confounding results.

Results of the current study also revealed smaller overall cingulate white matter volume (averaged across hemispheres) in SPD patients as compared with healthy controls; BPD patients exhibited a trend towards significantly reduced cingulate white matter volume compared with healthy controls, but no significant cingulate volume differences from SPD patients. Given these results and their potential impact on the primary finding of reduced cingulate FA in BPD patients, I was then able to control for volumetric effects and, thus, provide additional information when trying to interpret what role, if any, volume may play in interpreting the FA differences. That is, although FA is thought to estimate the orientation of axon bundles, it remains unclear what specific factors lead to abnormalities in FA, including whether or not contributions to anisotropy

should be attributed to axonal coherence (e.g., decrease in parallel diffusivity, increase in perpendicular diffusivity) and/or abnormal myelination caused by altered oligodendrocytes and/or oligodendrocyte expression (Alba-Ferrara & de Erasquin, 2013). In other words, because spatial resolution obtained by MR-DTI is at the macroscopic level, the molecular factors that underlie anisotropy remain elusive to date. Nonetheless, because we included volume in our analyses as a covariate (which prior DTI studies in these patients groups did not do), the current findings enable us to suggest that white matter volumetric effects were likely *not* a confounding factor when considering potential contributions to reduced FA in segments of the cingulate in BPD patients.

However, it should be noted that, contrary to our hypotheses, the SPD patients did not exhibit differences in cingulate FA compared to healthy controls or BPD patients. These results were unexpected, especially because the cingulate is part of the limbic circuitry, a network thought to play a major role in SPD symptomatology, including problems with social anxiety and isolation, odd beliefs/magical thinking, and unusual perceptual experiences. As such, it is possible to interpret the absence of group differences in cingulate FA within the context of prior work suggesting that SPD patients exhibit relative sparing of frontal regions compared with patients with schizophrenia (Siever & Davis, 2004), which may reflect a protective or modulatory factor that ultimately precludes the full development of schizophrenia and vulnerability to psychosis in SPD. Additionally, although our results are in line with prior work by Nakamura and colleagues (2005) reporting no significant group differences in SPD cingulate FA from healthy controls, they are somewhat incongruent with our group's prior finding of lower FA in posterior cingulate regions (BA's 23, 31) and higher FA in anterior cingulate

regions in SPD (BA 25; Hazlett et al., 2011). Interestingly, however, although we did not detect *significant* group differences in anterior and posterior cingulate FA, the same patterns reported previously by our group were also observed in the current study (SPD > HC FA in BA 25; SPD < HC FA in BA 23).

That being said, the primary SPD finding that did emerge from the present study showed that SPD patients exhibited smaller white matter volume of the cingulate (averaged across hemispheres) compared with healthy controls but not BPD patients. Similar to inferences made from FA findings, it is possible to argue that reduced white matter volume may suggest aberrant connectivity in this region. Nonetheless, these results are inconsistent with our group's prior findings using different samples that reported smaller relative anterior and posterior cingulate gray matter volume and larger relative anterior and posterior cingulate white matter volume in SPD patients compared with HC (Hazlett et al., 2008) and no SPD-HC group differences in anterior and posterior cingulate gray and white matter (Goldstein et al., 2009), respectively. Due to the current debate in the field regarding which methods are the most reliable and valid for analyzing white matter, as well as known challenges when trying to assess alterations in white matter volume given the subtlety of changes in this tissue type compared with gray matter volume, our group employed different strategies for analyzing white matter in the two prior studies mentioned above as compared with the current study. Specifically, whereas every slice of the cingulate was manually traced for the present study, the above-mentioned studies (e.g., Goldstein et al., 2009, Hazlett et al., 2008) utilized a semi-automated parcellation and segmentation program to analyze gray and white matter, which may help explain discrepancies. Further, it should be noted that the one study by

our group that did employ the same manual tracing methodology as the present study did not separate gray and white matter and failed to detect SPD-HC group differences in overall cingulate volume (Haznedar et al., 2004).

As highlighted at the start of this section, the present study's principal finding is that BPD patients exhibited significantly decreased FA in posterior cingulate white matter and marginally significantly decreased FA in anterior cingulate white matter, as compared with controls but not SPD patients. Although it remains difficult to characterize the exact implications of these findings, we can speculate that results reflect alterations in the normal branching of aspects of the cingulate gyrus, a region frequently implicated in BPD studies and thought to play a role in BPD symptomatology. As such, the present study's findings suggest that altered posterior *and* anterior cingulate white matter may contribute to some of the cardinal symptoms of BPD. Additionally, it is interesting to note that SPD patients exhibited a similar pattern to that of BPD individuals, highlighting a potential commonality among the two groups; however, their pattern was not significantly different from healthy controls.

Consistent with the hypothesis of aberrant posterior cingulate white matter connectivity in BPD, several functional neuroimaging studies with BPD patients have reported abnormal activation and glucose metabolic patterns in posterior cingulate while performing specific tasks (e.g., contrasting unresolved and resolved life events: Beblo et al., 2006; pain perception: Schmahl et al., 2006; Niedtfeld et al., 2012; Kluetsch et al., 2012; semantic and episodic memory retrieval: Mensebach et al., 2009; negative emotionality: see Ruocco, 2013 for review). Thus, our findings can also be interpreted within the context of work investigating the basic functions of the posterior cingulate.

Specifically, work has suggested its involvement in visuospatial orientation, navigation of the body in space, self-referential/reflective activity, language, and memory encoding and retrieval processes (Torta & Cauda, 2012), all of which have been implicated in neuropsychological studies with BPD patients (Beblo et al., 2006; Carter & Grenyer, 2012; Dinn et al., 2004; Harris et al., 2002; Kirkpatrick et al., 2007; Monarch et al., 2004; O'Leary et al., 1991; Stevens et al., 2004). Of note, given work showing selective interconnectivity between the posterior cingulate and parahippocampal formation in supporting episodic memory retrieval, results from the current study can also be related to several findings of BPD weaknesses with aspects of episodic and autobiographical memory (Reid & Startup, 2010). In this respect, it is also possible to interpret results of the current study within the context of research suggesting that posterior cingulate subserves specific aspects of emotional functioning (Torta & Cauda, 2012). For example, the posterior cingulate is thought to play an important role in the processing of affective pictures (Nielen et al., 2009), another area of functioning where BPD individuals evidence weaknesses (Hazlett et al., 2012; Limberg et al., 2011).

The present study also found lower FA in dorsal anterior cingulate white matter in BPD patients relative to HC, but these results only trended towards statistical significance. Nonetheless, it may also be helpful to highlight potential implications. First, research has shown that the dorsal aspects of the cingulum bundle are the most prominent (relative to its other components), which correspond to segments 4 and 5 of the current analyses (Mori, Wakana, Nagae-Poetscher, & van Zijl, 2005). Thus, the current study's finding of lower FA in dorsal anterior cingulate (segment 4) in BPD patients compared with healthy controls may reflect alterations of the cingulum which, in turn, may lead to

abnormal or decreased connectivity to and/or from the anterior cingulate. This idea would be consistent with work by Rüsch and colleagues (2010) reporting altered structural connectivity between the corpus callosum and dorsal segments of the anterior cingulate bilaterally in women with BPD and comorbid attention-deficit hyperactivity disorder compared with HC, as determined by a probabilistic diffusion tensor-based fiber tracking method.

Second, the current study's anterior cingulate findings are also consistent with research reporting anterior cingulate abnormalities in BPD. For example, several structural MRI studies have found reduced anterior cingulate gray matter volume in individuals with BPD (van Elst et al., 2003; Hazlett et al., 2005; Soloff et al., 2008). Also, several functional studies have revealed altered glucose metabolic rate in the anterior cingulate in the resting state (hypometabolism: De la Fuente et al., 1997; Goyer et al., 1994; hypermetabolism: Juengling et al., 2003) and abnormal anterior cingulate activation/deactivation during specific tasks (e.g., processing of fear stimuli: Minzenberg et al., 2007; emotion processing: Enzi et al., 2013).

Third, whereas research has yet to identify the exact mechanisms through which the dorsal anterior cingulate operates, it is known to have strong interconnections with regions frequently implicated in BPD, including lateral prefrontal cortex, parietal cortex, and premotor and supplementary motor areas. As such, the dorsal anterior cingulate, frequently characterized as the cognitive-related division of the anterior cingulate, has also been ascribed several functions for which BPD patients evidence weakness (Bush et al., 2000). For example, the dorsal anterior cingulate has been shown to play a role in attention-for-action/target selection, motivational valence assignment, motor response

selection, error detection/performance monitoring, competition monitoring, anticipation, working memory, novelty detection, and reward salience. It follows, then, that individuals with BPD demonstrate weakness across several of these areas, including cognitive and behavioral inhibition, decision-making, planning, memory, and reward salience (Bazanis et al., 2002; de Bruijn et al., 2006; Haaland and Landro, 2007; Maurex et al., 2009; Rentrop et al., 2008; Schuermann et al., 2011; Lawrence et al., 2010; Leyton et al., 2001; Dinn et al., 2004). Indeed, a review of 14 studies investigating BPD cognitive functioning found that 86% of the investigations reported dysregulated control abilities associated with motor, attention, and other impulsivity-related cognitive processes involving dorsal anterior cingulate (LeGris and van Reekum, 2006). In this respect, it is also interesting to note that some work has reported BPD difficulty on a flanker task specifically subserved by anterior cingulate (Fan and Posner, 2004; Leyton et al., 2001), as analysis of errors has suggested a pattern of impulsive tendencies and poor self-monitoring.

Taken together, results of the present study suggest that, compared with HC, BPD individuals exhibit white matter abnormalities in aspects of the posterior and anterior cingulate that are also exhibited by SPD patients but not to the same extent. As diffusion abnormalities only permit us to infer alterations, the results provide indirect support for the notion that BPD individuals display aberrant cingulum connectivity, which may be associated with some of the characteristic BPD neurobehavioral and cognitive weaknesses, such as problems with interpersonal skills and self-reflective activity, as well as poor error-detection, impulsivity/inhibition and other aspects of attention/executive functioning abilities. Specifically, it can be argued that decreased FA reflects poor

efficiency in information transition across these fibers, as the myelin and/or axonal alterations interfere with adequate timing of signals at the nodal links of a circuit. Although the exact neurobiological substrates underlying these alterations remain unclear to date, it is interesting to note that oligodendrocytes of associative white matter tracks are among the most metabolically active cells in the adult central nervous system and, as a result, are susceptible to the accumulation of metabolic damage (Kochunov et al., 2007). That said, it remains difficult to determine whether inferred myelin and axonal abnormalities in BPD are due to such damage to local factors and occur throughout development (e.g., factors responsible for the orderly arrangement of myelin sheaths and axonal trajectories such as cell migration, axon guidance) and/or are due to genetic variation in the NTRK1 gene, which has been linked with nervous system development and myelination and/or the OLIG2 gene necessary for oligodendrocyte generation (Alba-Ferrara & de Erausquin, 2013). Further, studies investigating anterior frontal cortex in schizophrenia, a different psychiatric patient population, also have reported decreased expression of two oligodendrocyte-associated proteins in schizophrenia, which may play a role in altered cingulate white matter in other psychiatric disorders such as BPD. Alternatively, if such white matter abnormalities do, indeed, contribute to some of the difficulties exhibited by individuals with BPD, it is also possible to argue that their etiology is multi-factorial and results from transactional relations amongst all of the factors discussed above (e.g., biological, genetic, and environmental).

Exploratory analyses were also performed to determine whether cingulate integrity was associated with clinical and neuropsychological factors in the patient groups. Initial findings revealed an unexpected pattern, as higher FA in posterior

cingulate was found to be associated with greater symptom severity in BPD as well as a higher level of stress-related paranoid ideation/dissociative symptoms. In addition, higher FA in anterior cingulate was associated with increased suspiciousness or paranoid ideation and flat affect in SPD participants. Clearly, these results run contrary to the overly simplistic notion that more FA is better and indicative of intact functioning (Alba-Ferrara & de Erausquin, 2013). However, it should be noted that increased FA has been reported in several studies examining individuals with schizophrenia and, as such, also has been proposed to reflect abnormality. Specifically, it has been argued that increased FA in schizophrenia is a result of neural overactivity in specific regions of the brain, resulting in deficient axonal pruning and, in turn, decreased efficiency in axonal transmission of information. In this respect, although our results were not congruent with initial hypotheses, they may still reflect cingulate involvement in some of the key BPD and SPD symptomatology, respectively. However, it should be noted that these statistically significant associations fell away once corrections were applied and thus may not reflect a true relationship. Potential reasons for the absence of findings include the idea that most of the clinical scales were self-report inventories and, therefore, may not adequately capture symptomatology. That is, individuals with personality disorders generally tend to be fairly ego-syntonic and, thus, may not endorse "symptoms" per se because their difficulties are more long-standing rather than acute in nature. Additionally, given the known phenomenological heterogeneity across BPD patients, it is also possible that variability in clinical profiles precluded the emergence of distinct symptom-FA patterns.

Results from preliminary analyses of the relationship between posterior cingulate integrity and both verbal and nonverbal memory performance also revealed unexpected findings, as lower FA was found to be associated with better performance on one of the CVLT learning trials and the short delay cued recall trial in BPD patients. Although these results are consistent with research showing anterior cingulate involvement in memory processes (Petit, Courtney, Ungerleider, & Haxby, 1998), they are inconsistent with our hypothesis that lower FA would reflect more abnormalities and thus, relatively weaker verbal memory performance. That said, it is important to keep in mind that, normatively, BPD performance on these CVLT trials was intact and, as such, lower recall was only "weak" relative to performance by BPD individuals with lower FA levels. Interestingly, Grant and colleagues (2007) also found a relationship between lower FA in anterior brain regions in BPD individuals and better performance on a verbal recognition task similar to the CVLT. Again, however, the exact significance of factors underlying FA patterns in DTI studies needs to be elucidated before any specific conclusions can be drawn regarding the potential role of cingulate white matter alterations in verbal memory performance in BPD individuals. Further, results from the current study's correlational analyses should be interpreted with caution as only a small subset of the study sample was administered the CVLT and could be included in the analyses. They also underscore the need for further research to investigate how FA abnormalities may or may not be related to specific BPD clinical and cognitive symptomatology.

Strengths, Limitations, and Future Directions

The most notable strength of the present study is that it was the first to investigate different aspects of the cingulum in both BPD and SPD, respectively. Further, it was also

the first to directly compare the integrity of these regions in two different personality disorder patient samples. Given the difficulties inherent in diagnosing disorders that do not always respect the boundaries imposed by DSM-IV diagnoses, the current study's direct comparison works to further our understanding of endophenotypic dimensions that both separate and cut across the current diagnostic categories. The present study was also unique in its inclusion of un-medicated patient groups without co-morbid Axis I and II disorders, as such factors frequently confound results in studies of personality disordered individuals. Similarly, in contrast with other DTI research with BPD and SPD patients, the current study included white matter volumetric analyses, thus improving our ability to understand the potential for volume differences to confound results and interpretation of the FA findings.

Despite these strengths, results reported in this study must be interpreted in the context of multiple methodological limitations. First, DTI measures average water diffusion within the image pixel volume; thus, volume averaging can become a source of error as the pixel size increases. Though prone to volume effects, DTI measures can contain other artifacts (e.g., bulk motion, spatial distortion). Also, this methodology can only be applied to the unidirectional portion of fiber bundles; it cannot pick up on fibers that intersect at non-parallel angles that other techniques (e.g., high angular resolution DTI) have improved upon. Third, the patients and HC participants were sex- and age-matched; however, white matter maturation continues into the fourth decade of life (Hasan et al., 2009; Lebel et al., 2008). Although the majority of maturational changes in the cingulum are presumably complete in the second decade of life, factors related to medication or psychopathology may delay/accelerate the maturation, and produce results

reflecting maturation process rather than integrity or orientation. Further, validity of the gray matter/white matter parcellation employed for the current study has not been confirmed by post-mortem work. Finally, the correlational analyses with cognitive data were significantly restricted by small sample sizes, thus increasing vulnerability to type 2 error.

Given the above-mentioned weaknesses, future studies should aim to include multi-modal imaging methods, such as high-resolution structural MRI, fMRI and DTI, to better understand the possible biological underpinnings and physiological significance of the present study's findings. In addition, it is crucial for future work to investigate the transactional relationships among white matter abnormalities, clinical phenomena, and cognitive functioning in these personality disorders, particularly through the use of longitudinal designs in order to help identify the different pathways and diagnostic outcomes to which they may lead. Finally, given evidence of similar patterns of white matter abnormalities between the patient groups, findings also highlight the need for empirical work to continue drawing direct comparisons of patients across each personality disorder and also within each personality disorder so as to better determine which neurobiological aspects cut across the categories and which are unique to subgroups of each disorder.

Conclusions and Clinical Implications

In summary, the current study provides evidence of aberrant connectivity of cingulum in BPD patients compared with HC, but not SPD patients. This finding is consistent with prior work reporting BPD cingulate abnormalities and suggests potential involvement of cingulate in BPD symptomatology. Indeed, given the proposed functions

of posterior and anterior cingulate, results can not only be considered within the context of their relation to core BPD symptomatology (e.g., problems with interpersonal relations, impulsivity, and disinhibition), they also can be explored as guides for tailoring treatment to better address the specific difficulties experienced by BPD patients. Consistent with other work suggesting a role for neurobiological factors in the conceptualization of BPD (rather than simply attributing difficulties to environmental factors such as trauma and family history), the current study stresses the importance of utilizing treatment modalities that directly address BPD weaknesses. For example, the finding of BPD alterations in aspects of the cingulate known to subserve error-monitoring abilities and cognitive inhibition provide strong support for the use of dialectical behavior therapy and its mindfulness module, which works to help the individual stay in the present moment as well as improve self-monitoring, inhibition, and attentional abilities.

Additionally, by directly comparing two personality disorders, the current study also contributes to the ongoing search for a more valid classification system of these disorders. The results revealed an interesting spectrum pattern of white matter alterations, providing support for the idea that personality disorder symptoms can be conceptualized as dimensional rather than categorical. That is, the current findings suggest a pattern of neurobiological factors that may be associated with underlying trait dimensions present across the diagnostic categories. In general, then, these results aid the current struggle to accurately capture the dimensional aspects of personality traits (rather than constraining samples to non-representative groups) by providing evidence of overlapping patterns/features that cut across the categories and, ultimately, working towards a better characterization of personality disorders and, in turn, more effective ways to treat them.

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