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# Cingulate and Temporal Lobe Fractional Anisotropy in Schizotypal Personality Disorder

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## Abstract

**Background—**Consistent with the clinical picture of milder symptomatology in schizotypal personality disorder (SPD) than schizophrenia, morphological studies indicate SPD abnormalities in temporal lobe regions but to a much lesser extent in prefrontal regions implicated in schizophrenia. Lower fractional anisotropy (FA), a measure of white-matter integrity within prefrontal, temporal, and cingulate regions has been reported in schizophrenia but has been little studied in SPD.

**Aims—**To examine temporal and prefrontal FA in 30 neuroleptic-naïve SPD patients and 35 matched healthy controls. We hypothesized that compared with healthy controls (HCs), SPD patients would exhibit lower FA in temporal and anterior cingulum regions but relative sparing in prefrontal regions.

**Method—**We acquired diffusion tensor imaging (DTI) in all participants and examined FA in the white matter underlying Brodmann areas (BAs) in dorsolateral prefrontal (BA44,45,46), temporal (BA22,21,20), and cingulum (BA25,24,31,23,29) regions using multivariate-ANOVAs.

**Results—**Compared with healthy controls, the SPD group had significantly lower FA in left temporal but not prefrontal regions. In the cingulum, FA was lower in the SPD group in posterior regions (BA31 and 23), higher in anterior (BA25) regions and lower overall in the right but not left cingulum. Among the SPD group, lower FA in the cingulum was associated with more severe negative symptoms (e.g., odd speech).

**Conclusions—**Similar to schizophrenia, our results indicate cingulum-temporal lobe FA abnormalities in SPD and suggest that cingulum abnormalities are associated with negative symptoms.

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**Declaration of Interest**
None.

**Keywords**

Diffusion tensor imaging; schizotypal personality disorder; dorsolateral prefrontal cortex; temporal lobe; cingulum; fractional anisotropy

Considerable evidence suggests white-matter abnormalities in multiple brain regions in patients with schizophrenia [1, 2]. In schizophrenia, disrupted white-matter integrity has been most consistently implicated in frontal, and temporal regions [3-11], as well as, alterations in the white-matter fibers connecting frontal and posterior areas (for review see [12]), such as the cingulum [13, 14], superior longitudinal fasciculus, corpus callosum [1], inferior longitudinal fasciculus [15], uncinate and arcuate fasciulus [16]. The meta-analysis of Ellison-Wright and Bullmore [3] concluded that across 15 studies, "significant reductions were present in two regions: the left frontal deep white matter and the left temporal deep white matter. The first region, in the left frontal lobe, is traversed by white matter tracts interconnecting the frontal lobe, thalamus and cingulate gyrus. The second region, in the temporal lobe, is traversed by white matter tracts interconnecting the frontal lobe, insula, hippocampus-amygdala, temporal and occipital lobe" (p. 3). Individuals with schizotypal personality disorder (SPD) have many similarities with schizophrenia patients, including shared genetics and biomarkers [17], providing support for a spectrum of schizophrenia disorders. As such, it has been suggested that the study of SPD, a personality disorder characterized by social isolation, odd behavior and thinking, offers a unique opportunity to study the pathophysiology and genetics of the schizophrenia spectrum without the confounding effects of hospitalization and medication that frequently limit interpretation of schizophrenia findings. Consistent with this model of schizophrenia-spectrum disorders, there is evidence that gray matter abnormalities in SPD [1, 18-21] resemble thosen revealed in schizophrenia. As a result, investigators are beginning to examine the degree to which white-matter abnormalities implicated in schizophrenia are also observed in SPD [22].

DTI is a magnetic resonance imaging (MRI) technique commonly used to examine white-matter tract areas by measuring the diffusion characteristics of water molecules and thus permitting us to infer the structural integrity of the tissue. The present study evaluated white matter integrity using a particular measure of diffusion, termed fractional anisotropy (FA). In white matter, FA is an index of the preferential diffusion of water parallel to the main fiber direction. The decreased anisotropy observed in schizophrenia is frequently assumed to reflect anomalous myelination; however, disrupted myelin is only one of several factors that influence anisotropy in white matter [23]. Deviations from parallel fiber arrangement (e.g., fibers oriented in multiple directions) are also reflected as decreased FA [23-25].

There are several reasons for evaluating frontal, temporal and cingulate white-matter integrity in individuals with SPD. First, a schizophrenia-spectrum model supports the notion that individuals with SPD will exhibit brain alterations similar to, although milder than those observed in schizophrenia. Since this hypothesis has been supported in our prior functional [26,27] and morphometric (volume) [20] neuroimaging studies of the schizophrenia spectrum, it is important to know whether it is also observed in studies examining FA.

Second, temporal and cingulate areas have been implicated in the key functional deficits of SPD. For example, SPD-associated gray matter volume reduction has been found in the superior temporal gyrus [20, 28-32], a region implicated in auditory processing [33] which is impaired in SPD [34]. Gray matter volume reductions have also been reported in other temporal cortex regions, such as Heschl's gyrus [35], middle temporal gyrus [20, 36] and inferior temporal gyrus [36], but less consistently [37]. Taken together, temporal gray matter findings suggest that individuals with SPD may also exhibit white-matter alterations in these regions.

The cingulate is implicated in SPD-related deficits because of its role in emotion, cognition and social functions [38, 39]. In the anterior (BA25 and BA24) and posterior (BA31, BA23, BA29) cingulate which serve distinct functions [39], SPD-related abnormalities have been reported. In particular, it has been suggested that anterior cingulate abnormalities may be associated with asociality, a core symptom of SPD [17]. We have previously reported reduced gray matter volume and increased white matter volume in BA24 of the anterior cingulate in individuals with SPD relative to HCs and schizophrenia patients [20]. The posterior division of the cingulate also modulates SPD-relevant functions including self-referential processing [40, 41], episodic memory [42-44] and visuospatial functions [45, 46]. We previously reported that SPD patients had higher relative glucose metabolic rates but normal volume in the left posterior cingulate compared with HCs [26]. Further, we reported that compared with HCs, individuals with SPD exhibited increased white matter volume in BA31 and BA23 [20].

The frontal lobe has also been implicated in studies of SPD because of its crucial role in executive function, working memory and attention, areas where individuals with SPD exhibit significant difficulties [47]. For example, individuals with SPD exhibit decreased blood oxygen level dependent (BOLD) activation of the left ventral prefrontal cortex and superior frontal gyrus, among other regions, during a working memory task [48]. However, frontal lobe volume findings in SPD have been inconsistent, and it has been suggested that this region of the brain may be relatively preserved in SPD compared with schizophrenia [20, 31, 49].

Only one previous study has examined FA in the cingulum bundle in individuals with SPD [22]. Reduced FA was found bilaterally in the uncinate fasciulus of neuroleptic-naïve SPD participants relative to HCs but no significant group differences were detected for the cingulum bundle. Of note, this study did not examine anterior and posterior regions of the cingulum separately. Additionally, reduced FA in the right uncinate fasciulus correlated with clinical symptoms, including ideas of reference, suspiciousness, restricted affect, and social anxiety. In contrast, left uncinate fasiculus FA was correlated with measures of cognitive function, including general intelligence, verbal and visual memory, and executive performance, as well as, negative symptoms.

The present study used FA as a measure of white matter integrity in a large, neuroleptic-naïve sample of SPD individuals and healthy controls. Given that we have previously published FA work in schizophrenia using a Brodmann-area approach (e.g., [56,57]), we thought it would be useful to apply this same methodology to SPD. FA values were averaged across lobes and combinations of BAs that were arranged based on neuroanatomical and theoretical assumptions. Compartmentalizing subcortical white matter according to cortical Brodmann areas not only facilitates a regional approach of the whole brain [58] and helps to avoid partial volume effects inherent in intrafascicular ROI placement but also allows for inferences to be made in regard to relationships among regional white matter FA and corresponding cortical BAs.

We hypothesized that SPD patients would exhibit reduced FA in the temporal and cingulate regions, consistent with reports of gray and white matter volume and FA abnormalities found in the schizophrenia-spectrum. However, we expected FA values in DLPFC regions of individuals with SPD to be more similar to HCs, representing relative sparing of these regions consistent with prior morphometric studies examining white matter volume. Consistent with this, we also hypothesized that among the SPD group, lower FA in temporal lobe and cingulum regions would be associated with greater symptom severity. Lastly, on an *exploratory* basis and to facilitate cross-study comparison of SPD and schizophrenia data, we calculated the HC-SPD effect sizes for FA in the 39 BAs for each hemisphere.

# Methods

## Participants

The sample comprised 30 individuals with DSM-IV diagnosed SPD (6 women and 24 men; mean age 41.4±10.7 years) and 35 HCs (11 women and 24 men; mean age 41.1±11.8 years). The HC and SPD groups did not differ in age or sex ($t(63)=-0.11$, $p=0.91$; $t(63)=-1.04$ $p=0.30$). We have previously reported on BA gray and white matter volume in a subset of these participants [20]. All HCs and the majority of the SPD participants (90%) were recruited through advertisement in local newspapers and local postings. The remaining SPD participants were recruited through referrals from outpatient clinics at the James J. Peters VA Medical Center and Mount Sinai Medical Center. None of the SPD patients had previously been hospitalized or taken antipsychotic medications. However, two of the 30 SPD patients had previously received psychoactive medications (1 received a benzodiazepine and 1 received a stimulant; both were discontinued by their physician ≥3 months prior to study enrollment). Participants provided written informed consent approved by the Institutional Review Boards of both institutions.

For all participants, the diagnosis was determined by doctoral-level psychologists who were specifically trained in the assessment of Axis II disorders. All participants received a full diagnostic structured interview which included the Structured Clinical Interview for DSM-IV Axis I disorders [50] and the Structured Interview for DSM-IV Personality Disorders [51]. In our group, the intraclass correlation for the SPD diagnosis is kappa=0.73.

To examine the clinical correlates of FA abnormalities in SPD we calculated the following symptom severity scores for each of the SPD patients: (a) Each of the nine DSM-IV symptom criteria for SPD was rated on a 4-point scale (0=absent, 0.5=somewhat present, 1.0=definitely present/prototypic, 2.0=severe/pervasive) and the total was calculated as an overall symptom severity score. 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; (b) Given prior work (e.g., [30]) showing a relationship between superior temporal gyrus volume and odd speech, we calculated odd speech impairment by adding the ratings for the six odd speech criteria subscales (each subscale was based on the 4-point scale described above) which included the following: (1) digressive, (2) vague, (3) over-elaborate, (4) circumstantial, (5) overly metaphorical, (6) not just digressive, vague, over-elaborate, but overly concrete, illogical or at an inappropriate level of abstraction; (c) Lastly, based on prior morphometric [20] and FA [22] work in SPD, we calculated a factor score for the negative/interpersonal symptoms of SPD (see [20] for more details) by totaling the scores for three of the SPD symptom criteria: odd thinking and speech (item 4), inappropriate or constricted affect (item 6), and social isolation (item 8).

Participants were also screened for severe medical or neurological illness and head injury by comprehensive medical history and laboratory tests taken by a physician. For all participants, history of significant head trauma, neurological disease, organic mental syndromes, significant medical illness, history of substance dependence, substance abuse disorder within the previous 6 months, any psychoactive medications in the last two weeks, or a positive urine toxicology screen for drugs of abuse on the day of the MRI was an exclusion criteria. SPD patients were also excluded if they met criteria for a past or present psychotic disorder or bipolar I. Healthy control participants had no history of an Axis I or II disorder and had no first-degree relative with an Axis I disorder.

## Image acquisition and processing

The structural and DTI sequences and image-processing were identical to those used in our prior studies involving large samples of patients with schizophrenia, e.g., [52]. $T_1$-weighted

MR images were acquired using a 1.5T Signa 5x scanner (GE Medical Systems) with a 3D-SPGR sequence (TR=24 msec, TE=5 msec, flip angle=40°, matrix size 256×256, field of view 23 cm, slice thickness 1.2 mm, total slices=124). The diffusion tensor sequence acquired fourteen 7.5-mm-thick slices (TR=10 s, TE=99 ms, TI=2.2 s, b=750 s/mm, δ=31 ms, Δ=73 ms, voxel size 1.8 × 1.8 × 7.5mm, FOV=230 mm, NEX=5). Before the diffusion EPI sequence, a Turbo Spin Echo was also acquired to obtain a localizing anatomical image. In order to solve for the components of the diffusion tensor, seven diffusion EPI images were obtained: six with different non-collinear gradient weightings and one with no diffusion gradient applied. The diffusion tensor for every voxel in a slice was computed by solving the seven simultaneous signal equations relating measured signal intensity to the diffusion tensor. Anatomical SPGR MR images were resectioned to the standard Talairach-Tournoux position using the algorithm of Woods et al[53] and a 6-parameter rigid-body transformation. The anisotropy images from each subject were then aligned to subject's own standard-position anatomical images using the same 6-parameter transformation. Eigenvectors and eigenvalues were computed for every tensor, creating the raw dataset for subsequent analyses. The eigenvector associated with the largest eigenvalue, or principal diffusivity, indicates the direction of the maximal apparent diffusivity, which in normal white matter corresponds to the orientation of the axis of an axonal bundle [52].

## Brodmann area (BA) analysis

We used our semi-automated parcellation technique based on the Perry post-mortem brain atlas (the atlas was published in Mitelman et al [55]). This method is an approximation to Brodmann-area parcellation and segmentation of gray and white matter which we have also previously employed in morphometric studies of SPD and schizophrenia [20,54]. The program divides manually traced coronal MRI brain slices into 20 radial and 10 midline sectors in each hemisphere, and each temporal lobe into 16 sectors. These sectors are then assigned to 39 Brodmann areas identified in the Perry atlas (BAs: 1-2-3-5, 4, 6, 7a, 7b, 8, 9, 10, 11, 12, 17, 18, 19, 20, 21, 22, 23, 24, 25, 27, 28, 29, 30, 31, 32, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, and 47). BAs 1, 2, 3, and 5 are combined into a single area because of the difficulties in their individual parcellation.

Segmentation into white and gray tissue types was done using the FSL program FAST with bias field correction of MRIs followed by kmeans clustering and local Markov analysis at each voxel. A binary image is created for each tissue types, which has received extensive methodological examination [59].

FA was averaged across white matter voxels underlying cortical Brodmann areas and was thus treated as a general tissue property with no reference to particular white matter tracts. This averaging allows for between-group comparisons of the integrity of regional white matter. Similarly, quantifying regional white matter volumes in reference to cortical Brodmann areas allows the between-group differences to be regionally delineated [52].

## Statistical analyses

We used two statistical approaches for our FA analysis. First, we selected *a priori* subgroups of Brodmann areas on a theoretical and anatomical basis and entered them into a series of analyses using multivariate analysis of variance (MANOVA) with Diagnostic group (HCs vs. SPD) as the between-group factor. We conducted a Group × Cingulum Brodmann area (BA25, BA24, BA31, BA23, BA29) × Hemisphere MANOVA with cingulum BA and hemisphere as the repeated measures. To test our fronto-temporal hypothesis, we conducted a Group × Lobe (frontal, temporal) × Brodmann area (Frontal: BA44, BA45, BA46; Temporal: BA22, BA21, BA20) × Hemisphere MANOVA. Group × Cingulum Brodmann area and Group × Lobe interactions and higher-order interactions were examined to establish

regional differences between groups. In reporting the repeated-measures MANOVA, means for the main effect of Diagnostic group were averaged (collapsed) across all of the repeated measures (e.g., lobe, Brodmann area, hemisphere). The Group × Cingulum region interaction entailed averaging means for each cingulum Brodmann area across the hemispheres for each of the groups. For the Group × Lobe interaction, the mean FA value for lobe was averaged across the three Brodmann areas within each respective lobe and the two hemispheres for each group. We report the multivariate *F* (Wilks Lambda) or univariate *F* with Greenhouse-Geisser adjusted probabilities and epsilon values from Statistica [60] for repeated-measure effects with more than two levels. Fisher's Least Significant Difference (LSD) tests were used to follow-up significant interaction effects with Diagnostic group. Our region-of-interest approach examines only the frontal lobe, cingulum, and temporal lobe with nested MANOVAs. This approach, which provided tests of hypothesized group differences, helps minimize Type I statistical error involved with *t*-tests for each area, group contrast, and hemisphere. It should be noted that age was not correlated with any of our primary dependent variables (FA in frontal or temporal lobe, FA in cingulum regions; or (in the SPD group) clinical symptom ratings) which is a prerequisite for conducting ANCOVA. Therefore, we did not conduct ANCOVA as it was not warranted. To facilitate comparisons between this study and our prior schizophrenia studies, e.g., [56,57], we report relative fractional anisotropy values. Relative FA values are expressed as: mean white matter FA within the Brodmann area/mean whole brain FA (averaged across gray and white matter).

Our second statistical approach was more exploratory and descriptive. Given the paucity of DTI studies in SPD, we thought it would be worthwhile for descriptive purposes to provide a more general regional map of where FA differed significantly between the groups. We conducted t-tests for all 39 Brodmann areas in each hemisphere ($p<0.05$) and present a statistical map of effect sizes.

Correlational analyses were limited to frontal and temporal regions where between-group differences in FA were significant. Pearson product-moment correlations were used to examine the association between FA in temporal and cingulum regions shown to be abnormal in the SPD group and clinical symptom severity.

## Results

### Cingulum

Compared with healthy controls (HC), the SPD group showed a pattern of lower FA in Brodmann area (BA) 31 and BA23 and higher FA in BA25 of the cingulate (Group × Cingulum BA interaction, $F(4,252)=2.69$, $p=0.046$, Greenhouse-Geisser) (Figure 1). Despite this significant interaction reflecting between-group differences in the pattern of FA within the five cingulum Brodmann areas examined (BA25, 24, 31, 23, and 29), none of the follow-up Fisher's LSD tests were significant (*p* values≥0.12).

Compared with the HC group, individuals with SPD had lower overall FA in the right hemisphere of the cingulate while the two groups looked more similar in the left hemisphere (averaged across all cingulum Brodmann areas; Group × Hemisphere interaction, $F(1,63)=5.41$, $p=0.02$, Wilks) **(**Figure 2**)**. Although this significant interaction indicates that the left-right pattern of FA was different between the groups, the Fisher's LSD tests for the left and right hemisphere were not significant (*p* values≥0.23). Neither the main effect of Group, nor any of the other interactions with group were significant.

### Frontal and temporal lobes

Compared with HCs, the SPD group had significantly lower FA in left temporal lobe (Fisher's LSD, $p=0.003$) while group differences in the frontal (dorsolateral prefrontal) lobe

were not significant (Fisher's LSD *p*-values were ≥0.62), Group × Frontal/Temporal Region × Hemisphere interaction, $F(1,63)=10.36$, $p=0.002$, Wilks (Figure 3).

### Group differences in FA within 39 Brodmann areas

To facilitate future cross-study comparisons, we conducted an exploratory analysis comparing HC-SPD differences in FA within the white matter of all 39 Brodmann areas in the left and right hemisphere and the effect sizes are shown in Figure 4. SPD patients had significantly lower FA in left hemisphere BA20, BA21, BA22, BA34, BA41, BA42 (note: left BA37 was $p=0.050$ and effect size=0.50) and right hemisphere BA23 and BA27.

### Symptom correlations

Given previous SPD work showing an association between negative symptoms and FA measures in the cingulum bundle [22], we examined symptom correlates of FA in brain regions where SPD patients and HCs showed significant FA differences (i.e. significant group interaction in MANOVA; cingulum and temporal lobe in each hemisphere). Consistent with the only other DTI paper in SPD [22], we examined the clinical symptom correlates of FA on an exploratory basis, with $p=0.05$ as the cut-off for reporting statistical significance, rather than using a correction for multiple correlations. Our rationale for this is that we wanted to replicate the work of Nakamura et al [22]. Greater severity of negative or interpersonal symptoms was associated with lower FA values in the left ($r=-0.38$, $p=0.04$; Figure 5A) and right cingulum ($r=-0.40$, $p=0.03$). Increased severity of odd speech was associated with lower FA in the left ($r=-0.43$, $p=0.02$, Figure 5B) and right cingulum ($r=-0.42$, $p=0.02$). None of the temporal lobe correlations reached significance.

## Discussion

Our results indicate white-matter alterations in temporal and cingulum regions in individuals with SPD compared with HCs. Compared with HC group, the SPD group had a different pattern of FA in the cingulum with higher FA in anterior regions (BA25) and lower FA in posterior regions (BA31 and BA23). SPD patients also had lower relative FA in the right but not the left cingulate. In the temporal lobe, the SPD patients had significantly lower overall FA in the left but not the right cingulum. No between-group differences in white matter FA were detected in the prefrontal regions we examined. It is not possible to determine from our study methods whether the between-group differences in FA reflect differences in myelination and/or axonal alignment. However, findings of decreased FA [61] together with myelin-related gene expression abnormalities [62] within the cingulate and temporal lobe in schizophrenia suggest that our finding of decreased FA in these regions in SPD may involve impaired axon-myelin interaction. It will be important in future schizophrenia-spectrum studies to use promising FA methods (e.g., [63]) which have begun to examine axonal differences and degree of myelination.

These cingulum FA findings extend our previous reports of abnormal gray and white matter cingulate volume and impaired left posterior cingulate function in SPD [20, 26]. The pattern of disrupted cingulum FA in the present study is complex but generally consistent with prior work in schizophrenia. Our finding of reduced FA in posterior cingulum (BA31 and BA23) is consistent with schizophrenia work showing similar reductions [4, 8, 11] and posterior cingulum is implicated in visuo-spatial function, memory function and self-referential processing which are areas where SPD individuals evidence deficiencies [65]. The finding of increased FA in anterior cingulum (BA25) is supported by work showing increased FA in left subgenual anterior cingulum white matter (and some other regions) in individuals at high genetic risk for schizophrenia [64]. Moreover, BA25 is part of the affect-related division

of the anterior cingulate and as such may be associated with restricted affect and interpersonal problems in SPD [17].

The cingulum bundle is the major tract connecting the frontal regions to parietal and limbic lobes. As reviewed in the introduction, cingulate regions play a critical role in functions that are impaired in individuals with SPD. Thus, our results suggest that altered white-matter in addition to gray matter pathology in these regions contribute to some of the cardinal symptoms of SPD. Consistent with this hypothesis, Nakamura and colleagues [22] found lower bilateral cingulum FA to be associated with more errors on executive function memory tasks in SPD. Further examination of the relationships between white-matter alterations and neuropsychological deficits in SPD should remain a goal in future studies.

Interestingly, the SPD patients showed a significant FA difference in the right cingulate but not the left. In contrast, both left and right cingulum FA disruptions have been reported in schizophrenia patients [4, 8, 11]. Considered together with these schizophrenia findings, our results provide some support for shared cortical deficits between schizophrenia and SPD but also offer hemispheric specificity for distinguishing white matter abnormalities in these two patient groups. Additionally, our findings can also be interpreted within the context of recent work suggesting that different processes are associated with the left and right cingulate, respectively. For example, Lutcke and Frahm [66] demonstrated bilateral distribution of error-related processes in the anterior cingulate in controls during a conflict-eliciting Go/No-Go spatial task but right-lateralized conflict-associated processing. In other words, right anterior cingulate, rather than left, may play a role in monitoring and resolving cognitive conflict during spatial tasks. However, work conducted by Stephan et al [67] revealed that left anterior cingulate may mediate cognitive control for conflict processing during verbal tasks, suggesting a possible dissociation between right and left anterior cingulate function for tasks that are explicitly verbal or spatial. Thus, our finding could be considered in terms of left vs. right anterior cingulate functions, implying that white-matter alterations of the right cingulum may be more closely associated with functional impairments in spatial processing rather than verbal. This possible explanation for our finding is in line with numerous studies reporting impaired spatial processing in SPD individuals [47, 48, 68]. Nonetheless, given that the functional significance of right vs. left cingulate is not well understood, it is important for future work to further investigate the hemispheric specificity of our results in SPD patients.

To the best of our knowledge, there is only one other study examining the integrity of cingulum white matter in SPD [22]. In contrast with our findings, Nakamura and colleagues [22] reported no SPD-related abnormalities in cingulum FA. This discrepancy may be due to differences between the studies in sample and/or methodological characteristics. For example, Nakamura et al [22] had a smaller sample size (n=15 vs. our sample size of n=30) and examined the cingulum bundle averaged across anterior and posterior cingulum regions. We examined regional FA differences in five Brodmann areas within the cingulum (BA25 and BA24 in anterior and BA31, 23, and 29 in posterior cingulate). However, it is important to note that our findings are consistent with Nakamura et al [22] in that we did not find a main effect of group for FA in the cingulum (HC vs. SPD FA averaged across all cingulum Brodmann areas and hemispheres).

Notably, we also revealed significantly reduced FA in the left temporal lobe of SPD patients as compared with controls. Furthermore, the exploratory analysis on all Brodmann areas displayed significantly lower relative FA in left temporal BAs 22, 21, 20, 41, 42 and 34 in SPD patients. Given the absence of between-group differences in prefrontal regions, these temporal lobe findings underscore the important role of temporal lobe regions in schizophrenia-spectrum disorders. These findings are consistent with previous work,

including our own, demonstrating reductions in superior (BA22) and middle (BA21) temporal gray matter regions in SPD [20, 29, 30]. Although the functional significance of these temporal cortical regions remains unclear, morphometric and functional investigations suggest that they may be involved in auditory and language processing deficits associated with SPD. Interestingly, Dickey and colleagues reported an association between *left* superior temporal gyrus volume and thought disorder in women with SPD [69]. In a later study, however, they reported a positive association between the clinical symptom of odd thinking/speech and abnormal *right* superior temporal gyrus activation while hearing deviant pitch tones in both men and women with SPD [34]. To help explain this discrepancy, Dickey et al [34] suggested a right hemisphere advantage for emotional aspects of language and prosody [70] and left hemisphere advantage for more semantic aspects of language. This notion of temporal lobe hemispheric specificity suggests that the present temporal white matter findings may be more closely associated with semantic aspects of speech in SPD.

We did not detect prefrontal FA differences between SPD patients and HCs, indicating that white matter abnormalities in SPD may be more localized to temporal and cingulate regions. This finding supports the idea that individuals with SPD may not exhibit the overt and sustained psychosis associated with schizophrenia due to intact prefrontal cortical circuits which may partially compensate for temporal and/or cingulate dysfunction [17].

Exploratory symptom correlates were examined to enable inferences regarding the functional impact of reduced cingulate and temporal lobe FA in SPD. SPD patients with greater negative symptom/interpersonal severity demonstrated lower FA in the cingulate. Similarly, a prior study reported an association between reduced cingulum FA and greater negative symptom severity in SPD [22]. We also found an SPD-related association between more severe levels of a specific negative symptom, odd speech, and greater reductions in cingulum FA. While these correlations are suggestive, further research is required to fully understand how FA abnormalities are related to specific symptoms in SPD.

Given that DTI technology is still in the early stages of its development, it is difficult to speculate on the implications of our findings, how they may arise and what contributions they may make to the pathophysiology of SPD. Myelination and axonal coherence are the major factors affecting FA. While myelin abnormalities are well documented, especially in schizophrenia [3], their cause remains unknown. Interestingly, a gene that is critical for myelination, neuregulin 1, has been identified as a susceptibility factor for both schizophrenia and SPD [71, 72]. Axonal coherence could be impacted by a variety of factors including local factors that maintain the orderly arrangement of axons as well as the developmental factors responsible for axonal trajectories, e.g., cell migration, axon guidance, and other forms of cell-cell interaction [25, 73].

By altering axonal conduction velocity, the myelin abnormalities associated with decreased FA would interfere with the optimal temporal convergence of signals at the nodal links of a circuit thereby comprising the circuit's function. Decreased FA associated with coherence could reflect local changes in the orderly arrangement of myelin sheaths, or increased heterogeneity of axonal trajectories. Increased FA, on the other hand, could influence decreased heterogeneity of axonal trajectories within the sampled voxels. Between-group differences in the heterogeneity of trajectories within a region could reflect differences in the relative numbers of axons with a particular origin or destination that course through a region. Thus, between-group differences in FA could reflect differences in anatomical connectivity.

### Strengths and weaknesses

Notable strengths of our DTI study include the largest SPD sample size examined to date and our novel findings of SPD-related abnormalities in cingulate and temporal lobe FA. However, the present study has limitations. Our scans were collected on a 1.5 T scanner which presents some methodological limitations. However, we selected a strategy of coregistering individual subject's MRI and DTI and as noted elsewhere [12, 56], the extent of error of coregistration and potentinal distortion of the diffusion tensor images from less distorted structural MRI was not large. The median difference of the absolute image frame coordinates of the anterior and posterior brain edges between structural and anisotropy images was 0.0 and 1.72 mm respectively and the median difference in brain length was 2.19 mm, just above 1%. The mean absolute value in mm of the differences between the diffusion tensor and MRI locations in the anterior and posterior brain edges was +2.12 and +2.68 mm respectively and means of signed differences were close to zero, indicating a lack of systematic bias. We did not have a schizophrenia comparison group or an "other" personality disorder group to compare with the SPD patients to examine the specificity of FA abnormalities. Future studies should use newer acquisition techniques and directly compare DTI measures along the schizophrenia spectrum: HCs vs. SPD vs. schizophrenia. Comparing SPD patients with other personality disorder groups that are not co-morbid with one another is also an important next step for determining the specificity of the present findings. Family psychiatric history on first-degree relatives of the SPD patients was not available. Thus, at present, it is not clear whether individual differences in white matter abnormalities among SPD patients are associated with positive family history for schizophrenia. Lastly, an anonymous reviewer noted that the idea of imaging a cluster of symptoms, wherein the particular symptoms may differ in any number of exponential ways and still derive a diagnosis of SPD is a limitation of this study. With the DSM currently under revision, there has been increasing criticism centered on the categorical approach to psychiatric diagnoses and several investigators (e.g., [74]) have argued that the next edition should embrace a dimensional view of psychopathology. In support of the recent NIMH Research Domain Criteria (RDoC) strategic plan which calls for studies to classify psychopathology based on dimensions of "observable behavior and neurobiological measures", we examined the dimensional aspects of SPD by conducting correlations between key clinical symptoms of SPD (i.e. a negative symptom/interpersonal factor score, odd speech) and the FA abnormalities we observed.

### Implications

Consistent with schizophrenia findings, our results indicate cingulum and temporal lobe white matter abnormalities in SPD and suggest aberrant neural networks or disconnectivity in SPD is associated with negative symptoms.

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## Research Highlights

- Compared with healthy individuals, schizotypal personality disorder patients showed lower fractional anisotropy (FA) in temporal and cingulate regions but not frontal regions.
- Among the SPD group, lower FA in the cingulate was associated with more severe negative symptoms including odd speech.
- Similar to schizophrenia, our findings indicate cingulate-temporal lobe white matter abnormalities in SPD and suggest cingulate FA abnormalities are associated with negative symptoms.

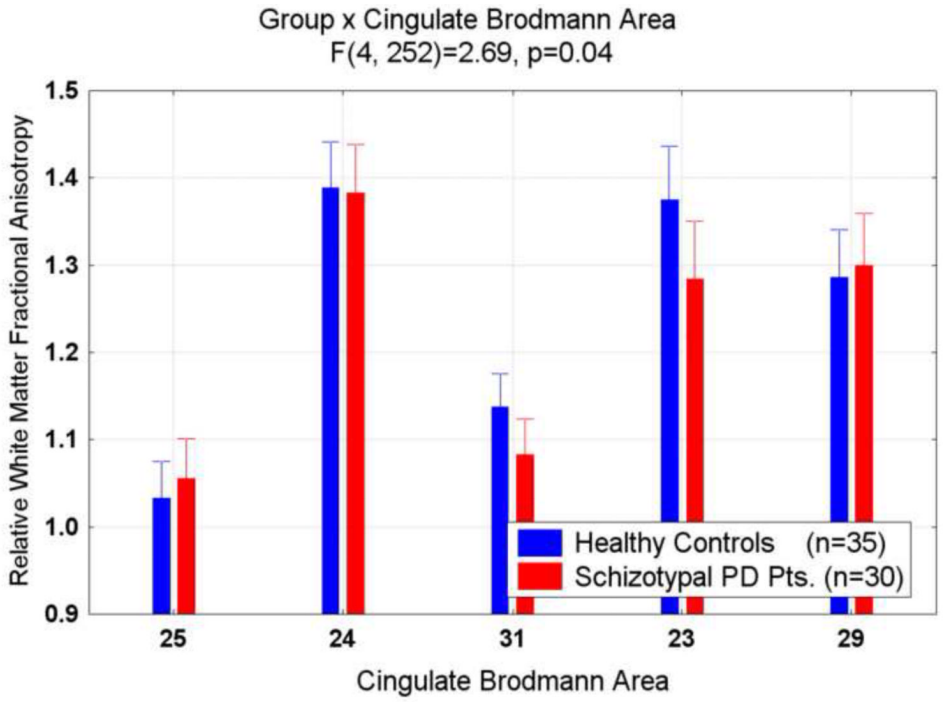


**Figure 1.**

Mean relative white matter fractional anisotropy (FA) values (BA white matter FA/whole brain FA (averaged across gray and white matter)) for the healthy control and SPD groups are shown within five Brodmann areas of the cingulum (BA25, 24, 31, 23, 29). Compared with healthy controls, SPD patients had lower FA in BA31 and BA23 (posterior cingulum) and higher FA in BA25 (anterior cingulum), Group × Cingulate Brodmann area interaction ($F(3.06, 192.9)=2.69$, $p=0.046$, Greenhouse-Geisser adjusted. None of the post-hoc Fisher's LSD tests were significant ($p$ values≥0.12).

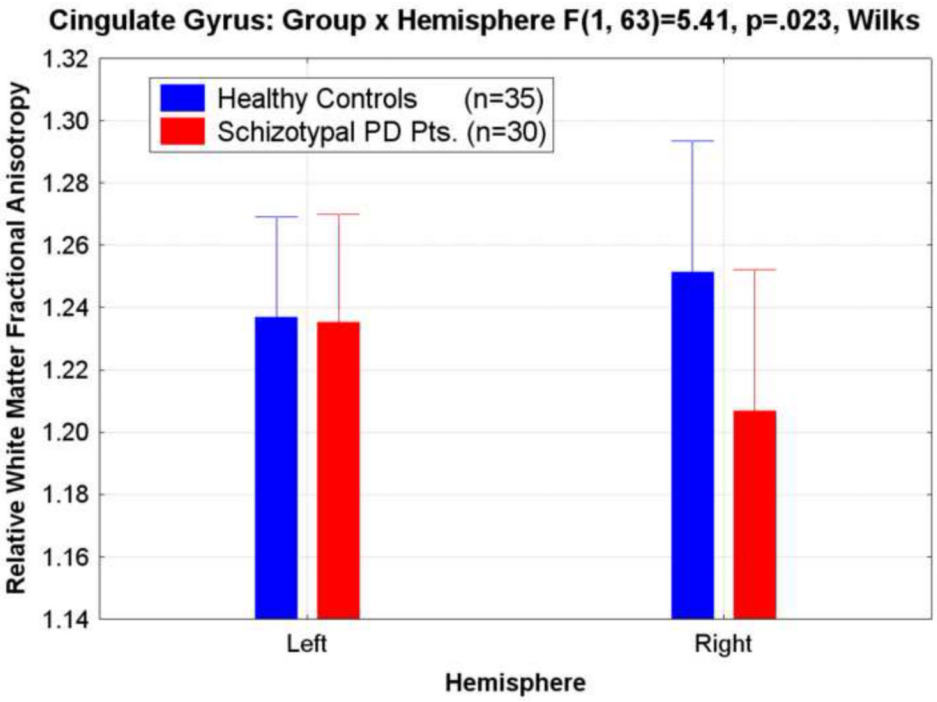


**Figure 2.**

Mean relative white matter fractional anisotropy (FA) for the healthy control and SPD groups is shown in left and right cingulum (averaged across the five Brodmann areas within the cingulum: BA25, 24, 31, 23, and 29). Compared with healthy controls, the SPD patients had lower FA in right but not left cingulum, Group × Hemisphere interaction, $F(1,63)=5.41$, $p=0.02$, Wilks. Neither post-hoc test was significant ($p$ values≥0.23).

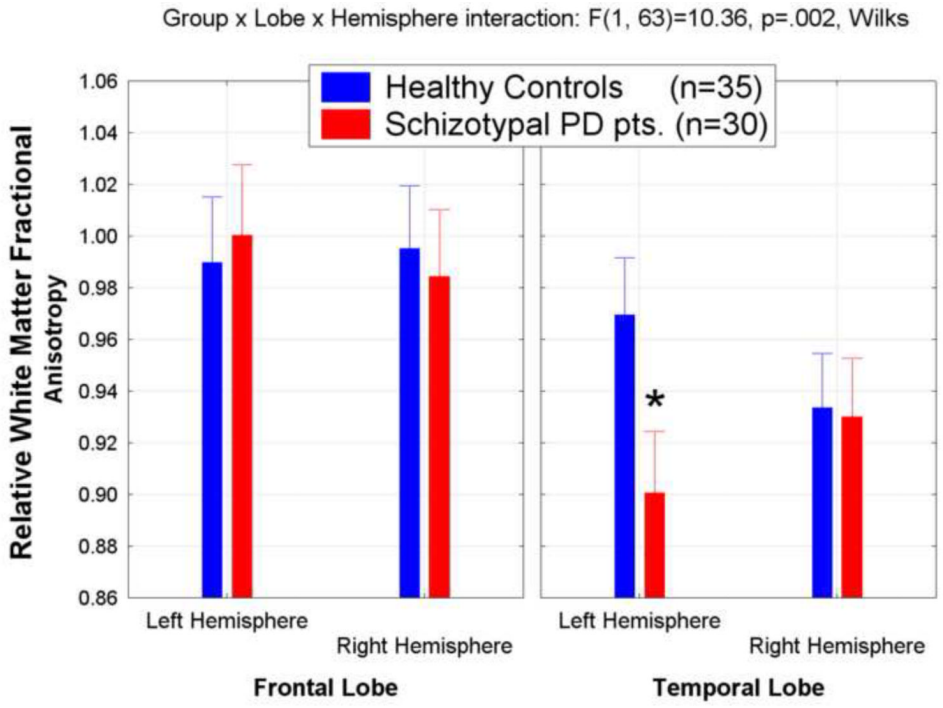


**Figure 3.**

Relative white matter fractional anisotropy (FA) in the healthy control and SPD group is shown in left and right dorsolateral prefrontral (averaged across BA44, BA45, and BA46) and temporal lobes (averaged across BA22, BA21, and BA20). SPD participants had significantly lower FA in left temporal lobe (*$p$=0.003, post-hoc Fisher's LSD) whereas FA differences in the frontal lobe were much less marked (Group × Lobe × Hemisphere interaction, $F(1,63)=10.36$, $p=0.002$, Wilks).

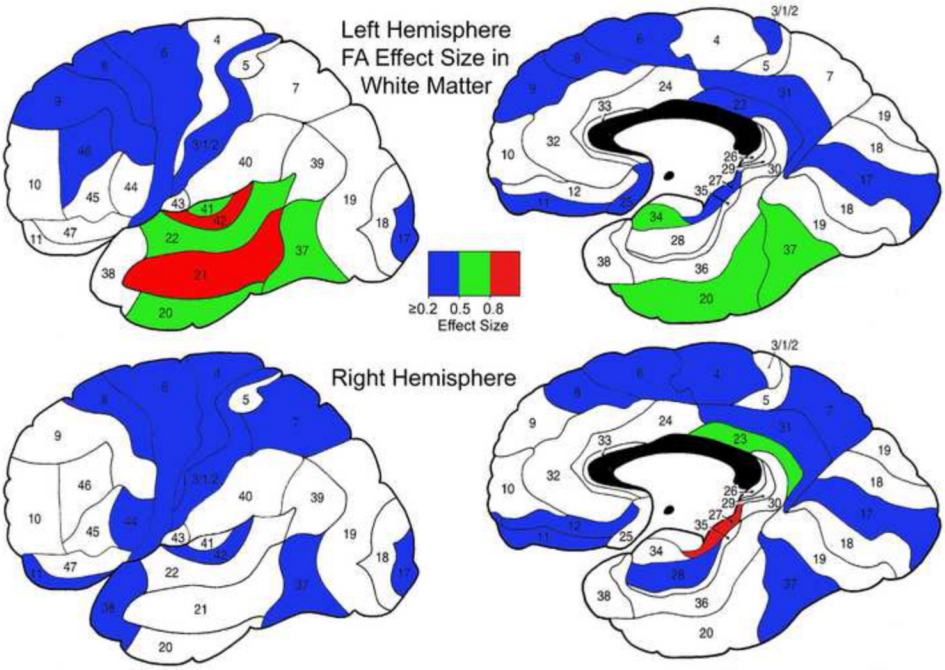


**Figure 4.**

Effect sizes for healthy control vs. schizotypal personality disorder (SPD) group differences in white matter of 39 Brodmann areas. White matter in red areas show a large effect size (Cohen's [75] d ≥ 0.8) where healthy controls > SPD, green areas indicate a medium effect size (d ≥ 0.5 and ≤ 0.79), blue areas indicate a small effect size (d ≥ 0.2 and ≤ 0.49), and white areas are d < 0.2.

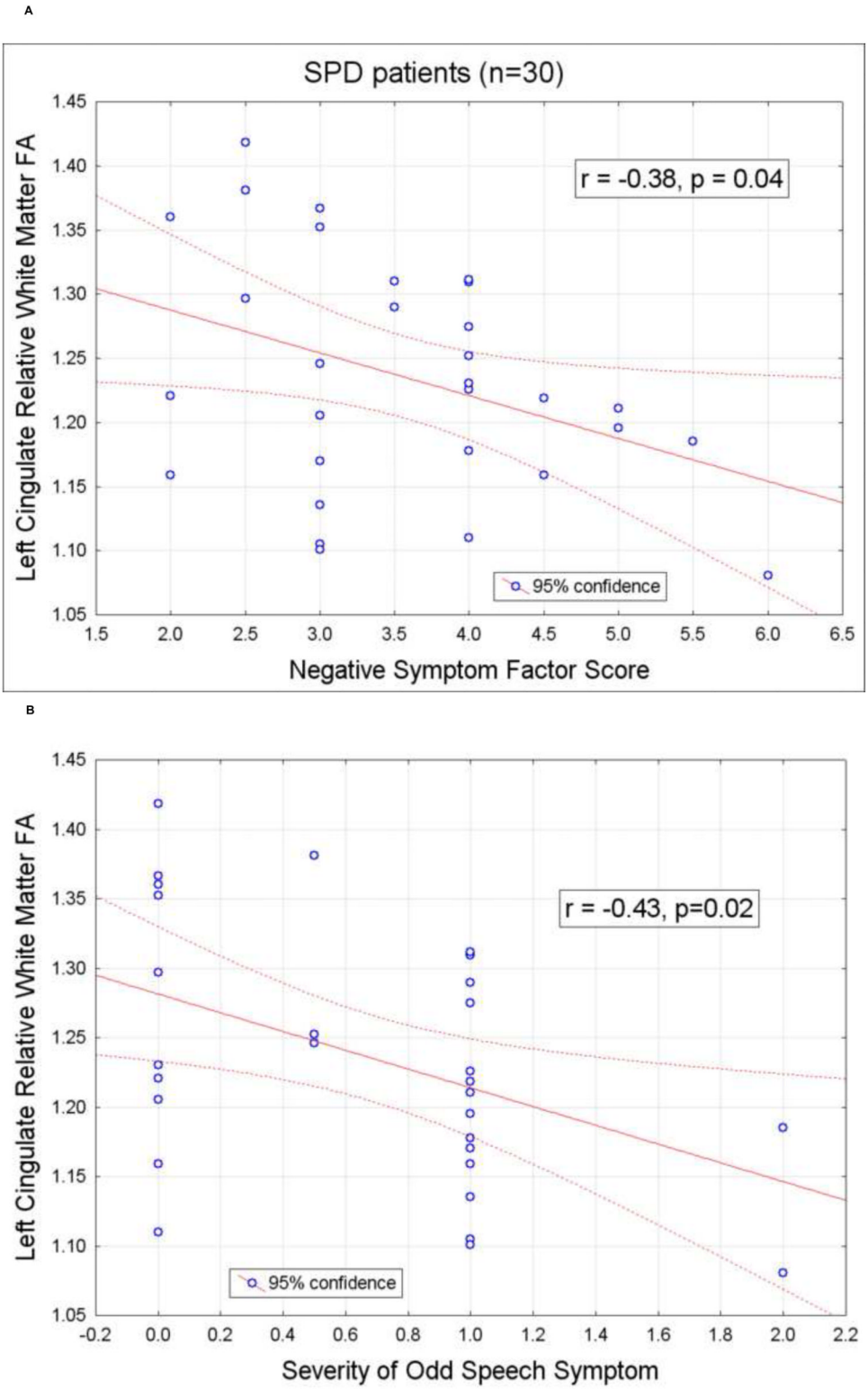


**Figure 5A-B. Clinical correlates of FA abnormalities in the cingulum**

*Greater* symptom severity (negative symptom factor score and odd speech) in schizotypal personality disorder (SPD) is associated with *lower* relative FA in the cingulate. **(A)** Scatter

plot is shown for the correlation between negative/interpersonal symptom severity and relative FA in left cingulum in the SPD group. **(B).** Scatter plot is shown for the correlation between the odd speech symptom severity score and relative FA in the left cingulum in the SPD group. Note that the correlations were also significant for the right hemisphere, see details in “Symptom correlation” section of the Results.

**Table 1**

Demographic and Clinical Characteristics of Healthy Controls and Schizotypal Personality Disorder (SPD) patients.

| Characteristic | Healthy Controls (n=35) | | | SPD patients (n=30) | | | *t* value | *p* value |
|---|---|---|---|---|---|---|---|---|
| | **Mean** | **SD** | **Range** | **Mean** | **SD** | **Range** | **HC vs. SPD:** | |
| Age (years): | 41.1 | 11.8 | 19-62 | 41.4 | 10.7 | 18-64 | t(63)= −0.11 | 0.91 |
| Education (years): | 14.7 (n=34) | 2.9 | 8-20 | 13.9 | 2.6 | 7-21 | t(62)=1.17 | 0.25 |
| Number of DSM-IV criteria for SPD dx: | - | - | | 6.58 | 0.92 | 5-8 | | |
| Sex: | **N** | % | | **N** | % | | | |
| Male | 24 | 69% | | 24 | 80% | | | |
| Female | 11 | 31% | | 6 | 20% | | t(63)= 1.04 | 0.30 |