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White Matter Integrity and Lack of Insight in Schizophrenia and Schizoaffective Disorder

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Abstract

Objective—Poor insight into illness is commonly associated with schizophrenia and has implications for the clinical outcome of the disease. A better understanding of the neurobiology of these insight deficits may help the development of new treatments targeting insight. Despite the importance of this issue, the neural correlates of insight deficits in schizophrenia remain poorly understood.

Method—Thirty-six individuals diagnosed with schizophrenia or schizoaffective disorder underwent diffusion tensor imaging (DTI). The subjects were assessed on two dimensions of insight (symptom awareness and attribution of symptoms) using the Scale to Assess Unawareness of Mental Disorder (SUMD). Level of psychosis was assessed with the Positive and Negative Syndrome Scale (PANSS).

Results—White matter abnormalities in the right superior frontal gyrus, left middle frontal gyrus, bilateral parahippocampal gyrus, adjacent to the right caudate head, right thalamus, left insula, left lentiform nucleus, left fusiform gyrus, bilateral posterior cingulate, left anterior cingulate, right cingulate gyrus, left lingual gyrus, and bilateral claustrum were associated with symptom unawareness. Misattribution of symptoms was related to deficits in the white matter adjacent to the right lentiform nucleus, left middle temporal gyrus, and the right precuneus.

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Contributors: Drs. Antonius and Hoptman were involved in the design and writing of the study protocol. Ms. Prudent, Rebani, D'Angelo and Drs. Antonius, Ardekani and Hoptman managed literature reviews and statistical analyses pertaining to the study. Ms. Prudent, Rebani, D'Angelo and Drs. Antonius, Ardekani, Malaspina and Hoptman were involved in the writing of various drafts and the final manuscript. All authors contributed to and have approved the final manuscript.

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Conclusions—Impaired insight in schizophrenia implicates a complex neural circuitry: white matter deficits in fronto-temporo brain regions are linked to symptom unawareness; compromised temporal and parietal white matter regions are involved in the misattribution of symptoms. These findings suggest the multidimensional construct of insight has multiple neural determinants.

Keywords

Diffusion Tensor Imaging; white matter; insight; awareness; frontal lobe; temporal lobe

Insight into illness is widely considered to be an important factor in coping with and treating schizophrenia (Amador & David, 2004). For this reason, there is considerable interest in understanding the underlying neural mechanisms of insight, which may have important implications for the development of future insight-oriented neuropsychiatric treatment. However, although extant research indicates a neurological etiology of insight deficits in schizophrenia (Pia & Tamietto, 2006; Shad et al., 2006b), the specific neural circuitry involved remains poorly understood.

Within clinical psychiatry, insight is commonly considered a multidimensional construct that refers to an individual's awareness of having a mental illness, understanding the need for treatment, awareness of the social consequences of mental disorder, and insight into specific psychopathological symptoms and ability to attribute these symptoms to a mental disorder (Amador et al., 1991, 1993). Diminished insight is associated with severity of psychopathology (Kemp & Lambert, 1995) and is more prevalent in schizophrenia compared to other psychotic disorders (Amador et al., 1994). Moreover, impaired insight poses a problem for adherence to treatment (Buckley et al., 2007; Lacro et al., 2002), prolongs duration of psychosis (Drake et al., 2000), and increases the risk for relapse, re-hospitalization (Drake et al., 2007) and involuntary status in the hospital (Kelly et al., 2004). Conversely, better insight into illness is related to better psychological coping mechanisms (Donohoe et al., 2004; Lysaker et al., 2003), as well as compliance with treatment and improved prognosis (Schwartz et al., 1997).

Early theories on the neurological etiology of insight deficits were partially based on the shared behavioral similarities between insight deficits in schizophrenia and the neurological disorder anosognosia (unawareness of deficits caused by brain injury). These theories focus on frontal, prefrontal (Amador et al., 1991), and right parietal lobe (David, 1990) deficits. More recent theoretical conceptualizations of insight in schizophrenia argue that the deficits are more complex, with various distinct brain areas implicated (David, 1999).

Neuropsychological studies largely support a relationship between poor insight and brain impairment in the frontal (Lysaker et al., 1998; Ritsner & Blumenkrantz, 2007; Young et al., 1993), and prefrontal and parietal lobes (Laroi et al., 2000; McEvoy et al., 1996), although the findings are inconsistent (Arduini et al., 2003; Cuesta & Peralta, 1994; Drake & Lewis, 2003; Freudenreich et al., 2004; Goodman et al., 2005; Kemp & David, 1996). In fact, reviews of neuropsychological studies suggest that the pathogenesis of insight deficits in schizophrenia is associated with impaired functioning in the frontal and parietal lobes, and these insight deficits are similar to impaired insight found in individuals suffering from anosognosia (Pia & Tamietto, 2006; Shad et al., 2006b).

Neuroimaging research provides further evidence for underlying brain impairment in insight deficits in schizophrenia. Brain studies on insight deficits implicate larger ventricular volume, in particular in the third ventricle (Takai et al., 1992), smaller total brain and intracranial size (Flashman et al., 2000), and frontal lobe atrophy (Laroi et al., 2000). Additionally, insight deficits have been associated with smaller right dorsolateral prefrontal

cortex (Shad et al., 2006a; Shad et al., 2004), and smaller bilateral middle frontal gyrus, right gyrus rectus, and left anterior cingulate gyrus volumes (Flashman et al., 2001). Imaging research also links insight deficits to reduced gray matter concentration in the left posterior cingulate, right anterior cingulate, bilateral inferior temporal regions including the lateral fusiform gyri (Ha et al., 2004), the right superior frontal gyrus, total inferior frontal gyrus, right orbitofrontal gyrus, and total prefrontal region (Sapara et al., 2007).

Three imaging studies found no significant correlations between lack of insight and total ventricular volume (David et al., 1995), grey and white matter volumes (Bassitt et al., 2007; Rossell et al., 2003), and cerebrospinal fluid and total brain matter volumes (Rossell et al., 2003). In a longitudinal study on insight improvement, one study found that patients with better insight showed increased activation in the left medial prefrontal cortex and right lingual gyrus (Lee et al., 2006). Two imaging studies report on the attribution of the psychiatric symptoms to a mental disorder; misattribution of symptoms were linked to larger right medial orbitofrontal cortex (Shad et al., 2006a) and smaller superior frontal gyrus volumes (Flashman et al., 2001).

Using a voxel-based morphometry approach to specifically examine insight sub-factors and grey matter volumes in patients with schizophrenia or schizoaffective disorder, Cooke et al. (2008) found correlations between: higher awareness of problems and increased regional grey matter volume in the left precuneus; higher symptom re-labeling and greater absolute grey matter in the right superior temporal gyrus; and, better awareness of and attribution to illness and greater regional grey matter in the left superior-middle temporal gyrus, the right inferior temporal gyrus, and the lateral parietal gyri. A fourth sub-factor, the awareness of need for medication, was not found to correlate with grey matter volumes. More recently, Palaniyappan et al. (2010) used high resolution MRI to examine the white matter volume of the posterior insula, specifically, and found that lower surface area and white matter volume of the right posterior insula, but not the left, was related to reduced insight.

Taken together, the neuroimaging and neuropsychological findings support a neurological etiology of insight deficits in schizophrenia (with some similarities to anosognosia). The distribution of impaired brain regions suggests that the insight deficits may be due to a disruption in neural circuitry, as compared to distinct brain region impairment. Thus far, neuroimaging studies on insight in schizophrenia have utilized either computed tomography (David et al., 1995; Laroi et al., 2000), structural magnetic resonance imaging (sMRI; Cooke et al., 2008; Flashman et al., 2000, 2001; Ha et al., 2004; Palaniyappan et al., 2010; Rossell et al., 2003; Sapara et al., 2007; Shad et al., 2006a, 2006b; Takai et al., 1992) or functional MRI (Lee et al., 2006) techniques. To further advance our understanding of the neural circuitry involved in impaired insight in schizophrenia, we employed diffusion tensor imaging (DTI) to study white matter integrity, which provides information on the organization and integrity of white matter.

Method

Participants

Participants were selected from a larger, ongoing neuroimaging study of white matter abnormalities in schizophrenia, which was approved by the Nathan S. Kline Institute for Psychiatric Research/Rockland Psychiatric Center Institutional Review Board and the Rockland County Department of Mental Health Institutional Review Board. All participants provided written informed consent prior to participation.

Thirty-six patients were included in the analysis. Demographic information is presented in Table 1. All patients met DSM-IV diagnostic criteria for schizophrenia (n=32) or

schizoaffective disorder (n=4) as confirmed by the Structured Clinical Interview for DSM-IV Axis I Disorders – Patient Edition (First et al., 1998). Patients were excluded if they met SCID-I/P criteria for substance dependence (lifetime), or substance abuse within the six months prior to study enrollment. Patients with neurological disorders or history of head trauma with loss of consciousness greater than 15 minutes were also excluded.

Procedure

Clinical Ratings—Insight into illness was measured using the Scale to Assess Unawareness of Mental Disorders (SUMD; Amador & Strauss, 1990). The SUMD is a twenty-item scale used to assess a patient's insight based on three dimensions: 1) general awareness of mental illness (including awareness of his or her current and past mental disorder, achieved effects of medication, and social consequences of mental disorder); 2) awareness of psychiatric symptoms, and; 3) attribution of symptoms, which refers to the degree to which he or she attributes the psychiatric symptoms to mental illness. Each item is rated on a Likert-type scale from 0 to 5. General and symptom awareness are rated using the following anchor points: 0=Cannot be assessed/item not relevant, 1=Aware (subject believes that he or she is mentally ill and suffers from psychiatric symptoms), 3=Somewhat (unsure, but can entertain the idea of mental illness/psychiatric symptoms), and 5=Unaware (does not believe he or she suffers from a mental illness or psychiatric symptoms). Attribution of symptoms are rated: 0=Cannot be assessed/item not relevant, 1=Correct (symptom is related to mental disorder), 3=Partial (considers possibility that symptom is due to mental disorder), and 5=Incorrect (believes symptom is not related to mental disorder). For the purpose of this study, we focused on current symptoms only and a mean score was calculated and used for analyses. Following traditional scoring of the SUMD (Amador & Strauss, 1990), we did not use weighted scores. Also, because the general items assess different dimensions of insight function, which may complicate interpretations, we focused (similarly to other studies; e.g., Shad et al., 2006) only on awareness of psychiatric symptoms and attribution of symptoms¹.

Current psychiatric symptomatology was assessed with the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987), which consists of thirty items rated from 1 (absence of psychopathology) to 7 (severe psychopathology). The scale is divided into positive, negative, and general items. Because the SUMD addresses symptoms that are also included on the PANSS, both scales were administered during the same session. SUMD items were only rated if the symptom was rated as present on the PANSS. Both scales were administered by trained study personnel.

Neuroimaging—Scanning was performed on a 1.5T Siemens Vision System (Erlangen, Germany) at the Center for Advanced Brain Imaging at the Nathan Kline Institute. Patients received an inversion-prepared T1-weighted scan (TR=11.6ms, TE=4.9ms, TI=1122ms, matrix=256×256, FOV=320mm, NEX=1, slice thickness = 1 mm, 190 slices, no gap), as well as a turbo dual spin echo scan (TR=ms, TE=22/90ms, matrix=256×256, FOV=240mm, slice thickness = 5mm, 26 slices, no gap), and a DTI scan (TR=6000ms, TE=100ms, matrix=128×128, FOV=300mm, NEX=7, slice thickness = 5mm, 19 slices, no gap) acquired in an oblique axial plane parallel to the anterior commissure – posterior commissure line. The b value for the DTI scan was 1000 s²/mm. Eight noncollinear diffusion sensitization directions were used (Jones et al., 1999).

Postprocessing: Fractional anisotropy (FA) was calculated using software written by one of the authors (BAA). The FA images were transformed into Talairach space using methods

¹Analyses pertaining to the general SUMD items are available upon request.

described elsewhere (Ardekani et al., 2003). The b_0 images were corrected for susceptibility induced distortion and were transformed into MNI space using methods described elsewhere (Ardekani et al., 2003; Hoptman et al., 2004). Images were matched to a template in MNI space, and the final voxel size was $1 \times 1 \times 1 \text{ mm}^3$. A white matter mask was computed from the mean spatially normalized patient FA image using a nonparametric image segmentation algorithm (Otsu, 1979) and was applied to all of the standardized images. This approach limited the voxels to white matter and resulted in fewer statistical comparisons, thereby lowering the probability of false positive tests.

Data Analysis: Because FA is negatively correlated with age (Pfefferbaum et al., 2000; Salat et al., 2005), we computed partial correlations on a voxelwise basis, controlling for age. Partial correlations were tested for significance using *t*-tests. We converted our *t*-maps and corresponding degrees of freedom maps to *p*-maps using custom software. From the *p*-maps we computed the *p*-value (corresponding to $p = .0036$ for Symptom Misattribution and $p = .0041$ for Symptom Unawareness) that would yield a false discovery rate (FDR) of 5% using FSL's *fd*r program. To further protect against Type-I error, we selected a minimum cluster size of 50 voxels (50 mm^3). The thresholded correlation maps were superimposed onto the T1-weighted template using AFNI software (Cox, 1996).

Results

Correlations between Clinical Variables

Pearson bivariate correlations were conducted to investigate associations between SUMD and PANSS variables (descriptive information on the clinical variables is presented in Table 1). A significant relationship emerged between the PANSS insight item "Judgment and Insight" and the SUMD subscales (symptom awareness: $r = 0.65$; attribution: $r = 0.74$; both $p < 0.01$), suggesting convergent validity. The analyses also revealed a significant relationship between the PANSS total score, when controlled for the insight item "Judgment and Insight" (excluded from the analyses), and SUMD symptom awareness, $r = 0.37$, $p < 0.05$, indicating that subjects with higher levels of overall psychosis symptoms exhibited poorer insight. A marginal relationship emerged between the PANSS total score, controlled for the PANSS insight item, and SUMD attribution, $r = 0.30$, $p = 0.10$. PANSS positive symptoms subscale correlated significantly with both SUMD subscales (symptom awareness: $r = 0.50$; and attribution: $r = 0.74$; both $p < 0.01$), suggesting that psychosis symptoms such as delusions and hallucinations may play a particularly important role in insight deficits. No correlations were revealed between PANSS negative/general subscales and the SUMD subscales.

Chi-square statistics revealed no significant gender and ethnicity differences for PANSS total and subscale scores and SUMD subscale scores.

Neuroimaging Correlations

The neuroimaging results revealed significant correlations between fractional anisotropy (FA) values and the SUMD symptom unawareness and misattribution of symptoms in multiple regions. These data are presented in Table 2 and 3, and Figures 1 and 2.

Discussion

The present study utilized DTI to investigate the brain regions involved in insight deficits in individuals diagnosed with schizophrenia or schizoaffective disorder. Using a multidimensional classification of insight our findings suggest that white matter deficits in

fronto-temporo brain regions are linked to symptom unawareness, and reduced white matter integrity in temporal and parietal regions is involved in the misattribution of symptoms.

Symptom Unawareness

Our imaging results for symptom unawareness implicate a complex network of fronto-temporal brain regions. Many of the regions are also involved in memory, cognitive, and emotional processing, suggesting a possible complex interplay between impairment in these areas and insight into specific psychiatric symptoms. Given the range of factors covered under symptom unawareness, including positive (e.g. delusions, hallucinations), negative (e.g. alogia, flat affect), cognitive (e.g. poor attention, confusion/disorientation), and other behavioral symptoms (e.g. poor control of aggressive and sexual impulses), a complex neural network is not unexpected.

In our study, the patients with poor insight into their symptoms demonstrated reduced FA in several frontal lobe regions, including the left middle and right superior frontal gyri. This finding is in support of other studies that have found the frontal lobe (Lysaker et al., 1998; Ritsner & Blumenkrantz, 2007; Young et al., 1993), particularly the prefrontal cortex (Sapara et al., 2007; Shad et al., 2004), to be a central brain region for insight in schizophrenia. As frontal lobe abnormalities underlie social cognitive deficits in schizophrenia (Yamada et al., 2009), poor insight might be mediated by cognitive deficiencies (Shad et al., 2006b).

The temporal lobe is also important to symptom awareness. We found reduced white matter integrity in the bilateral parahippocampal gyrus and the left fusiform gyrus in the patients with poor insight into their symptoms. This may suggest that memory processing is a key feature in symptom awareness as the temporal lobe is important for working memory processing (Schon et al., 2009), and the parahippocampus is involved in non-verbal memory for successful decision making (Harrington et al., 2004). This finding supports other research that speculates a connection between poor insight and deficits in executive working memory (Shad et al., 2007). Thus, it is possible that in people with schizophrenia, deficits in temporal lobe regions underlie impaired processing of memories related to psychiatric symptoms and the ability to make decisions about the psychiatric illness.

Furthermore, our findings indicate that symptom unawareness is related to deficits in white matter in or near the cingulate (left/right posterior, left anterior and right cingulate gyrus), the right thalamus, the right caudate head, the left insula, the left/right claustrum, and the left lentiform nucleus. The cingulate connects with the hippocampus and prefrontal cortex and is involved in a variety of cognitive processes such as affective processing, learning and memory. In patients with schizophrenia, several studies have shown that the anterior part of the cingulate is reduced (Baiano et al., 2007), and reports have speculated that the anterior cingulate and other paralimbic structures are important in the pathophysiology of the disease and in the mechanisms of insight (Ha et al., 2004; Shad et al., 2007).

The caudate and the lentiform nucleus are part of the basal ganglia, which projects to the prefrontal cortex and is involved in executive functions, learning and memory (Graybiel, 1995). As the basal ganglia is connected to the medial temporal lobe (Packard & Knowlton, 2002), deficits in the caudate and lentiform nucleus regions may add to the impaired memory processing that negatively affects insight into psychiatric symptoms. The basal ganglia is also connected to the thalamus, which is considered to be a relay station for sensory processes, but also believed to be a central region implicated in attention and consciousness (Newman, 1995). The thalamus may therefore be important in relaying physiological and psychological changes to the frontal cortex, while reduced white matter

integrity surrounding the thalamus may impair the connectivity between the thalamus and the frontal cortex thus compromising awareness of psychiatric symptoms.

Because of the complexity of examining the *combined* awareness of various different psychopathological symptoms that potentially have distinct neurological underpinnings, the data should be interpreted with some caution. Future research studies designed specifically to examine the neural correlates of the *individual* psychopathological symptoms will help to clarify the neural pathways involved in insight deficits and further advance the field.

Symptom Misattribution

The ability to attribute psychiatric symptoms to mental illness requires some level of awareness (Shad et al., 2007). However, as our findings and those of others (Flashman et al., 2001; Shad et al., 2006a) suggest, there appear to be different neuroanatomical bases for symptom awareness and symptom attribution. In contrast to other studies (Flashman et al., 2001; Shad et al., 2006a), we did not find symptom misattribution to be related to frontal lobe impairment. Instead, our findings implicate lower FA in white matter near the right precuneus, the right lentiform nucleus, and the left middle temporal gyrus.

The precuneus is located in the parietal lobe and research suggests its involvement in self-consciousness (Cavanna & Trimble, 2006). Being conscious of one's self is expectedly important for initial evaluation of any changes in mental state to then subsequently search for attributable factors for those changes. In schizophrenia, hypoactivation in the precuneus has been related to poor procedural learning (Kumari et al., 2002). The middle temporal gyrus and the lentiform nucleus (as previously discussed, part of the basal ganglia) are both involved in memory processing. The involvement of temporal lobe regions in misattribution of psychiatric symptoms suggests that memory and recognition of psychiatric symptoms are important aspects of successful attribution of symptoms; an individual with schizophrenia must be able to compare and process memory of their past health to their current illness in order to identify the factors that are responsible for illness severity. Although we did not find direct evidence of frontal involvement, it should be added that some of the white matter regions in which we found correlations are in pathways that may include frontal projections. A tractography approach, in which the pathways that pass through these regions could be visualized, would be particularly useful in this regard.

Positive Correlations

We found that higher FA values was associated with higher awareness of symptoms in the left supramarginal gyrus, left/right inferior parietal lobule, right middle frontal gyrus, left subthalamic nucleus, and right culmen. These results suggest greater white matter integrity in these regions was related to reduced insight. This finding was unexpected and difficult to explain, possibly due to methodological limitations. One possible explanation is that increased FA may represent loss of crossing fibers, thus resulting in less complex neuronal networks. We may also surmise that with the various regions of the brain having the same process of neuronal deterioration, some areas present more parallel distribution and thus reduced complexity. Another explanation may be that the positive correlations are due to the complexity of insight. Future studies specifically examining the positive correlations between insight deficits and FA are needed.

Limitations

There are several limitations with this study that bear discussion. We included both patients with schizophrenia and schizoaffective disorder in the study. As both disorders are heterogeneous, future studies should examine insight deficits in more homogeneous schizophrenia groups. Also, future imaging studies may want to compare insight into illness

to self-reflective abilities (i.e., metacognition) as research shows that poor insight is closely related to impaired self-awareness (Koren et al., 2004; Lysaker et al., 2005), and recent fMRI research has begun to identify the neural circuitry for impaired awareness of self (and others) in schizophrenia (Murphy et al., 2010). Additionally, all our subjects were chronic schizophrenia patients at a state psychiatric hospital, which may suggest more severe psychotic symptoms and poorer insight than what is typically found in outpatients. This may have confounded the results, and it is important that future DTI research also examines groups (e.g., outpatients) with lower levels of symptoms. Although all our subjects were on antipsychotic medication, we did not analyze medication effects on insight ratings and imaging processing. To fully examine the role of medication effects on the neurobiology of insight, one will need to enroll first-episode or early-course schizophrenia patients. Similar to other imaging studies examining brain white matter and insight in schizophrenia (e.g., Palaniyappan et al., 2010) we did not include a healthy comparison group, thus limiting conclusive interpretations of the specificity of our imaging findings. Images were acquired on a 1.5 Tesla scanner and had a 5 mm slice thickness, and at the time the study took place our DTI scans had a very high signal-to-noise ratio (SNR). However, thinner slices can now be collected at higher field strength to optimize SNR and resolution in DTI protocols.

Conclusions

Having insight into one's own illness and understanding of the consequences of the disease and need for treatment is an important part of a successful prognosis in people with schizophrenia. Neuroimaging and neuropsychological research suggest a neurological etiology of insight deficits, which may have implications for treatment. We used DTI to examine white matter integrity and its correlation with insight into illness in people with schizophrenia. We found that poor awareness of psychiatric symptoms was linked to compromised white matter integrity in various fronto-temporo brain regions. Misattribution of symptoms was related to reduced FA in parietal and temporal brain regions. These findings indicate that impaired insight in schizophrenia implicates a complex neural circuitry, which involves various cognitive and memory systems.

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Figure 1. Sagittal view of fractional anisotropy and awareness of symptoms (SUMD Items 4-20). Notes: Every 5th slice is shown from left to right hemisphere. Blue = significant negative correlations. Yellow = significant positive correlations. Data thresholded for a False Discovery Rate of .05, $p = .0041$.

Figure 2. Sagittal view of fractional anisotropy and attribution of symptoms (SUMD Items 4b-20b). Notes: Every 5th slice is shown from left to right hemisphere. Blue = significant negative correlations. Yellow = significant positive correlations. Data thresholded for False Discovery Rate of .05, $p = .0036$.

Table 1

Demographic and clinical information.

N	36
Age (mean age in years)	37.4 (SD: 10.5)
Sex¹	Female: 9 Male: 27
Ethnicity¹	Black/African-American: 18 White: 16 Other: 2 Hispanic: 5
Diagnostic subtypes	Schizophrenia Paranoid: 16 Disorganized: 2 Undifferentiated: 12 Residual: 2 Schizoaffective Bipolar: 2 Depressed: 2
PANSS Total mean score	78.5 (SD: 17.1)
PANSS Positive subscale mean score	19.3 (SD: 6.0)
PANSS Negative subscale mean score	20.5 (SD: 6.2)
PANSS General subscale mean score	38.7 (SD: 8.4)
PANSS Judgment and Insight (G12)	4.4 (SD: 1.3)
SUMD Symptom awareness (item 4-20 mean score)	3.5 (SD: 1.1)
SUMD Attribution awareness (item 4b-20b mean score)	4.1 (SD: 1.1)

Table 2

Location of significant correlations between fractional anisotropy and awareness of symptoms (SUMD Items 4-20).

Nearest GM Location ^{1,2}	Size	Talairach Coordinate ³	t-value ⁴
Negative Correlations			
R superior frontal gyrus	318	13, 51, -2	-4.43
L middle frontal gyrus	112	-32, 43, -1	-4.66
L parahippocampal gyrus	112	-14, -14, -13	-4.25
R parahippocampal gyrus	820	33, -44, -6	-4.56
R parahippocampal gyrus	200	12, -10, -10	-4.98
R caudate head	177	9, 7, -1	-3.94
R thalamus	514	23, -29, 3	-4.20
L insula	98	-44, -19, 3	-4.01
L insula ⁵	284	-33, 23, 18	-4.37
L lentiform nucleus	933	-28, -21, 4	-4.52
L lentiform nucleus	90	-17, -8, 0	-3.80
L fusiform gyrus	323	-48, -27, -19	-4.13
L posterior cingulate	299	-18, -45, 12	-4.23
R posterior cingulate	214	8, -38, 16	-3.89
L anterior cingulate	108	-17, 50, -2	-3.70
R cingulate gyrus	170	14, -10, 32	-3.58
R cingulate gyrus	141	22, -44, 24	-4.06
L lingual gyrus ⁶	116	-31, -66, -3	-3.57
L claustrum	267	-25, 16, 6	3.67
L claustrum	139	-34, -5, -9	-3.89
R claustrum	203	31, -7, 11	-4.03
Positive Correlations			
L supramarginal gyrus	91	-35, -48, 28	4.61
L inferior parietal lobule	107	-30, -27, 27	4.99
R inferior parietal lobule	101	37, -37, 36	3.82
R middle frontal gyrus	104	23, 33, 2	4.36
L subthalamic nucleus	642	-12, -12, -3	5.11
R culmen	115	21, -35, -21	5.36

Notes:

¹ GM=Gray Matter,

² L = Left, R = Right,

³ Talairach coordinate of maximum of correlation cluster,

⁴ maximum of cluster,

⁵ left Brodmann area 13,

⁶ left Brodmann area 19. Data thresholded for a False Discovery Rate of .05, p = .0041.

Table 3

Location of significant correlations between fractional anisotropy and attribution of symptoms (SUMD Items 4b-20b).

Nearest GM Location ^{1,2}	Size	Talairach Coordinate ³	t-value ⁴
Negative Correlations			
R lentiform nucleus	276	15, -6, -7	-4.52
R precuneus	272	20, -48, 33	-4.44
L middle temporal gyrus	111	-41, -49, -2	-4.01
No Positive Correlations			

Notes:

¹ GM=Gray Matter,

² L = Left, R = Right,

³ Talairach coordinate of maximum of correlation cluster,

⁴ maximum of cluster. Data thresholded for a False Discovery Rate of .05, p = .0036.