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Cigarette Smoking and White Matter Microstructure in Schizophrenia

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Abstract

The majority of patients with schizophrenia smoke cigarettes. Both nicotine use and schizophrenia have been associated with alterations in brain white matter microstructure as measured by diffusion tensor imaging (DTI). The purpose of this study was to examine fractional anisotropy (FA) in smoking and non-smoking patients with schizophrenia and in healthy volunteers. A total of 43 patients (28 smoking and 15 non-smoking) with schizophrenia and 40 healthy, non-smoking participants underwent DTI. Mean FA was calculated in four global regions of interest (ROIs) (whole brain, cerebellum, brainstem, and total cortical) as well as in four regional ROIs (frontal, temporal, parietal and occipital lobes). The non-smoking patient group had a significantly higher IQ compared to the patients who smoked and our results depended on whether IQ was included as a covariate. Without IQ correction, significant between-group effects for FA were found in four ROIs: total brain, total cortical, frontal lobe and the occipital lobe. In all cases the FA was lower among the smoking patient group, and highest in the control group. Smoking patients differed significantly from non-smoking patients in the frontal lobe ROI. However, these differences were no longer significant after IQ correction. FA differences between non-smoking patients and controls were not significant. Among smoking and non-smoking patients with schizophrenia but not healthy controls, FA was correlated with IQ. In conclusion, group effects of smoking on FA in schizophrenia might be mediated by IQ. Further, low FA in specific brain areas may be a neural marker for complex pathophysiology and risk for diverse problems such as schizophrenia, low IQ, and nicotine addiction.

Keywords

Diffusion Tensor Imaging; Nicotine; Fractional Anisotropy

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1. Introduction

Individuals with schizophrenia smoke cigarettes at a much higher rate than in the general population (Hughes et al., 1986). However, the biological mechanism for this phenomenon is unknown. The self-medication hypothesis (Dalack et al., 1998) is supported by research showing that nicotine improves negative symptoms and cognitive performance in patients with schizophrenia (Dalack et al., 1998; Lyon, 1999; Barr et al., 2008; Jubelt et al., 2008). Alternatively, illness-related changes in neural networks may confer a predisposition for nicotine addiction.

Over the past decade, numerous research studies have utilized diffusion tensor imaging (DTI) to investigate the pathophysiology of schizophrenia (White et al., 2008). DTI measures white matter microstructure (Basser et al., 1994), which can shed light on the underlying connectivity between brain regions. A commonly used metric in DTI studies is fractional anisotropy (FA), which estimates the degree to which tissue organization limits diffusion of water molecules in brain white matter (Basser and Pierpaoli, 1996). DTI studies have consistently identified lower FA in various white matter regions in schizophrenia patients, especially within the frontal and temporal lobes, cingulum bundle, and corpus callosum reviewed by (White et al., 2008).

Given the high prevalence of smoking in schizophrenia, most of the schizophrenia DTI findings to date likely reflect patients that are chronic smokers. Emerging data suggest that cigarette smoking is associated with higher FA in specific brain regions in healthy individuals (Jacobsen et al., 2007; Paul et al., 2008), but the relationship between smoking and FA in patients with schizophrenia has been an area in need of research.

In this study, we accessed an existing dataset acquired through the MIND Consortium Study. This large, multisite neuroimaging study was designed to examine the neurobiology of first-episode and chronic schizophrenia on brain structure and function. Because it included a subgroup of patients who did not smoke, this sample provided the opportunity to explore neural correlates of smoking in schizophrenia. In order to examine a sample that had equal numbers of smokers and non-smokers from each site, we included participants from the University of Iowa and the University of New Mexico sites. The purpose of this study was to examine FA across three groups: smoking and non-smoking patients with schizophrenia and healthy controls. Based on prior work, we predicted that the two schizophrenia groups would have lower FA than the control group. However, based on the existing data on smoking in healthy individuals in which FA was higher in smokers, and in support of the “self-medication” hypothesis, which would predict a beneficial effect of smoking, we predicted that the patients with schizophrenia who smoke would have higher FA than the non-smoking schizophrenia group.

Since cognitive measures such as intellectual functioning (as estimated by intellectual quotient; IQ) commonly reveal impaired functioning in patients with schizophrenia, and since prior work has revealed relationships between IQ and FA (Schmithorst et al., 2005; Deary et al., 2006; Yung et al., 2007; Chiang et al., 2009; Kontis et al., 2009; Li et al., 2009), we anticipated that IQ may be an additional important factor in the analysis. Thus in addition to the primary aim of examining FA across the three groups, we explored the impact of IQ on FA for each of the three groups, and examined the relationships between FA and smoking with and without correction for IQ.

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2. Materials and Method

2.1 Subjects

The participants represent a subgroup of the MIND Consortium Study, in which DTI data and smoking histories were obtained. The parent study had recruited participants from four sites: Massachusetts General Hospital (MGH) and the Universities of Iowa, Minnesota (Minn) and New Mexico (NMex). For additional information on this study, we refer the reader to our previous publications (Segall et al., 2009; White et al., 2011). In the present study, we included subjects only from the NMex and Iowa sites in order to reduce inter-site variability, and to ensure similar numbers of smokers in the groups from each site. Life-time exposure to smoking was recorded for all participants. For participants that reported a history of smoking, pack-years of smoking were calculated.

The study was approved by the institutional review boards for each site, and subjects were enrolled after providing written informed consent. All subjects underwent a diagnostic assessment that included either the structured clinical interview for the DSM-IV (SCID) (First et al., 1997) or the comprehensive assessment of symptoms and history (CASH) (Andreasen et al., 1992). Positive and negative symptoms were rated using the scale for the assessment of positive symptoms (SAPS) (Andreasen, 1984) and the scale for the assessment of negative symptoms (SANS) (Andreasen, 1983). Intelligence quotient (IQ) was estimated using the block design and vocabulary subtests of the Wechsler adult intelligence scale – 3rd Edition (Wechsler, 1997). Depression symptoms were assessed using the Calgary Depression Inventory (Addington et al., 1992). Extrapyramidal side effects were assessed using the Simpson Angus Scale (Simpson and Angus, 1970) and the Abnormal Involuntary Movement Scale (AIMS) (Lane et al., 1985).

Healthy volunteers were recruited from community postings. Exclusionary factors included (1) a physical or neurological disorder affecting brain function (i.e., head injury, seizure disorder); (2) a lifetime history of any axis I psychiatric disorder, including substance abuse or dependence; or (3) a diagnosis of schizophrenia or bipolar disorder in a first-degree relative. Participants in the control group all denied history of smoking cigarettes (i.e., pack-years equivalent to 0). None of the controls and none of the non-smoking patients had a lifetime history of either substance abuse or substance dependence. Among the smoking group there were 8 subjects with a past history of alcohol abuse, 1 with a past history of barbiturate dependence in the past, 1 with a past history of opioid abuse, 2 with a past history of cocaine dependence, 3 with a past history of amphetamine abuse, 5 with a past history of hallucinogen abuse, 2 with a past history of THC dependence, and 5 with a past history of THC abuse.

2.2 Image Acquisition

The high resolution structural images were acquired at all sites with a slice thickness of 1.5 mm, an in-plane resolution of 0.625×0.625 mm, and flip angle = 7°. NMex utilized Siemen's 1.5 Tesla scanner with TR = 12, TE = 4.76, and NEX = 1. Iowa utilized a 1.5 T Siemens scanner with a TR = 20, TE = 6, and NEX = 3. Three separate images were collected and averaged at both sites

All DTI data were acquired with slice thickness = 2 mm and in-plane resolution of 2×2 mm. Iowa utilized a Siemens 3 Tesla with TR = 9500, TE = 90, B values of 0 and 1000, NEX = 4 and 6 directions. NMex utilized a Siemens 1.5 Tesla with TR = 9800, TE = 86, B values of 0 and 1000, NEX = 4 and 12 directions.

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2.3 Image Processing

The T1-weighted anatomical images were analyzed using BRAINS2 (Roiz-Santianez et al.; Magnotta et al., 2002; Hill et al., 2009; Sanches et al., 2009). The structural image was segmented to yield a skull-stripped T1-weighted image and a white matter mask. The skull-stripped T1-weighted image was co-registered with an AC-PC aligned atlas image using a rigid body registration after the atlas was scaled to the size of the subject's brain. The Talairach parameters were defined for the subject based on an affine registration of the atlas image into the raw subject space allowing the Talairach atlas to be warped onto each subject. The T2 weighted image was then co-registered with the AC-PC aligned T1 weighted image. A previously validated multi-modal tissue classification was then performed (Harris et al., 1999).

The diffusion weighted images were analyzed using the GTRACT program (Cheng et al., 2006). Images were first co-registered to the b0 image using a mutual-information image registration to correct for motion and distortions caused by eddy currents. The images were median filtered and the diffusion tensor was estimated. FA was then calculated for all subjects.

The b0 image was then co-registered with the skull-stripped T1 weighted anatomical image from BRAINS2 using a rigid body transformation and a mutual information similarity metric. Next, a B-Spline transform was applied to remove distortion in the echo-planar images resulting from susceptibility changes at air tissue interfaces (Cheng et al., 2006). The resulting transforms were applied to the scalar maps, placing them into the space of the anatomical image.

2.4 Image Analysis

Using a region of interest (ROI) approach, utilizing Talairach parameters (Collins et al., 1994; Andreasen et al., 1996) we measured FA within white matter of several major areas of the brain. The first three regions were global: total brain, cerebellum, brainstem, and total cortical (which included the entire cortex). We also separately examined regions within the cortex: including the frontal, temporal, parietal, and occipital lobes (see Figure 1). The white matter ROIs were defined as the intersection between the tissue classified as white matter by BRAINS2 segmentation and the FA map with a threshold of 0.1. This eliminated regions of signal loss resulting from magnetic susceptibility differences.

2.5 Statistical Analyses

Demographic measures were examined using an ANOVA or χ^2 analyses to assess for group differences. To account for site-related differences, FA measures for each individual and each ROI were converted to z-scores within site and combined for group analyses (White et al., 2011). To evaluate FA differences among groups, a one-way ANCOVA was performed on the z-transformed data. Since there was a trend age difference between the groups (p = 0.07), and since age affects FA (Barnea-Goraly et al., 2005; Salat et al., 2005; Mukherjee and McKinstry, 2006; Giorgio et al., 2009), age was used as a covariate. Post-hoc, pair-wise ANCOVAs were then performed on measures where a significant ($p \leq 0.05$) group difference was present on the primary test. To assess the relationship between pack-years and FA in smoking patients in brain areas that showed group differences, Spearman rank order correlation coefficients were used since measures of pack-years of smoking fit a non-linear distribution.

The second set of analyses was designed to assess the additional impact of IQ on findings. Prior DTI studies in various populations that have detected significant relationships between IQ and FA (Schmithorst et al., 2005; Deary et al., 2006; Yung et al., 2007; Chiang et al.,

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2009; Kontis et al., 2009; Li et al., 2009). Therefore in this study we conducted analyses to examine the relationships between IQ and FA within each group. Additionally, prior schizophrenia research studies have found lower mean IQ of about one standard deviation in groups of patients with schizophrenia (White et al., 2006; Mesholam-Gately et al., 2009). Furthermore, research has suggested an inverse relationship between smoking and IQ (Modig et al., 2011). Thus, with regard to between-group comparison of FA, since the relationships between smoking, IQ, schizophrenia and brain white matter are still unknown, we believed it important to include analyses both with and without adjusting for IQ. We speculated that neural abnormalities could influence an array of outcomes (lower IQ, schizophrenia, risk for smoking addiction), in which case correction for IQ is not appropriate. However, if smoking were to impact FA causally, it would be important to correct for IQ in order to understand the impact of smoking above and beyond that of IQ.

3. Results

3.1 Demographic and Clinical Variables

Demographic information for the three study groups are provided in Table 1. The groups were well matched on sex, handedness and parental education. However, there was a significant group difference for estimated IQ ($F(2,78)=16.55$, $p<0.0001$), in which the smoking patient group had the lowest scores. Table 2 describes demographic and clinical variables for the groups separately for each site. Similar proportions of groups were recruited from each site (chi square= 1.74, $p=0.419$). The only overall difference (for the three groups) on these variables between sites was higher levels of maternal education at the Iowa site ($t(78)=2.33$, $p=0.02$). When examining site differences within each group, there was a significant difference for IQ in the non-smoking schizophrenia group, in which non-smoking patients from Iowa had higher IQs then non-smoking patients from NMex ($F(1, 12)=8.53$, $p=0.0128$.

Table 3 describes clinical variables comparing the two schizophrenia groups. The smoking and non-smoking schizophrenia patients were well-matched on measures such as positive, negative, or disorganized symptoms, length of illness, medication history, and movement rating scales (Table 3). However, non-smoking patients displayed more depressive symptoms than smokers at a trend level ($p=0.09$). At the time of scanning, most of the patients were taking prescribed medications. In the non-smoking group, medications included risperidone ($n=4$), aripiprazole ($n=3$), quetiapine ($n=1$), olanzapine ($n=2$), and clozapine ($n=1$). Among the smoking group, medications included risperidone ($n=5$), aripiprazole ($n=2$), quetiapine ($n=2$), olanzapine ($n=3$), clozapine ($n=9$), fluphenazine ($n=1$, and haloperidol ($n=2$). Antipsychotic dose years (1 dose year = 100 chlorpromazine equivalents per day for one year (Berndt et al., 2000) for the patient groups are provided in Table 3.

3.2 FA and Smoking Group

FA values for each region in each group and each site are reported in Table 5. A one-way ANCOVA of the three groups with age as a covariate revealed significant group differences in the following white matter ROIs: total brain ($F(2,79)=4.93$, $p=0.001$), total cortical ($F(2,79)=5.87$, $p=.001$), frontal ($F(2,79)=5.57$, $p=0.006$), and occipital ($F(2,79)=4.06$, $p=0.02$) (see Table 4 and Figure 2). Analyses were also repeated with both age and sex as covariates and the findings remained significant. When analyses were repeated on these measures with IQ correction, group effects were no longer significant: total brain ($F(2, 79)=2.35$, $p=0.10$), cortical ($F(2,79)=1.98$, $p=0.14$), frontal ($F(2,79)=2.13$, $p=0.12$), and occipital ($F(2, 79)= 2.99$, $p=0.056$).

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Post hoc one-way ANCOVA tests were performed for ROIs that showed a group difference on the main tests (whole brain, cortical, and frontal). Similar to our previous study (White et al., 2008), when comparing all 50 schizophrenia patients together to healthy controls, the patients had lower FA in all three ROIs (total brain: (F(1,87)=6.94, p=0.003); cortical: (F(1,87)=10.47, p=0.002); frontal lobe: (F(1,87)=11.62, p=0.001). These findings withstood IQ correction (total brain (F(1,85)=4.43, p=0.03); cortical (F(1,85)=4.61, p=0.03); frontal (F(1, 85)=3.62, p=0.03).

We next sought to compare FA between smoking and non-smoking patient groups (see Table 4). FA was significantly lower in the smoking patient group for the frontal ROI (F(2, 40)=4.12, p=0.049). This pattern was present at a trend level in three other ROIs: total brain (F(2, 40)=2.98, p=0.09), cortical (F(2,40)=3.7, p=0.06), and occipital (F(2,40)=2.95, p=0.09). After correcting for IQ, these differences were no longer significant. Finally, when comparing non-smoking patients to controls, no significant differences were found for FA in any ROIs, with or without IQ correction.

3.3 FA and Pack-Years

Within patient smokers, no relationship was detected between pack-years and FA in any of the ROIs, with or without IQ correction.

3.4 FA and IQ

Since IQ clearly impacted findings, we conducted within-group correlation analyses between IQ and FA in ROIs where group differences were observed. Within the control group, no correlations were observed between FA and IQ. Among smoking patients, IQ was significantly and positively correlated with FA in the frontal (r=0.62, p=0.0007), cortical (r=0.51, p=0.008) and parietal (r=0.46, p=0.02) ROIs. IQ was not correlated with pack years among patients in the smoking group. Among non-smoking patients, IQ correlated with frontal FA at a trend level (r=0.42, p=0.09). When patient groups were examined together, IQ was correlated with FA in total brain (r=0.31, p=0.05), cortical (r=0.39, p=0.01), frontal (r=0.51, p=0.0008), and parietal (r=0.36, p=0.02).

4. Discussion

This study evaluated the relationship between FA and smoking in patients with schizophrenia. This is the first study to examine inter-relationships among the combined factors of schizophrenia, smoking status, IQ, and white matter microstructure. As hypothesized, we report that patients with schizophrenia (smoking and non-smoking) had lower FA than the control group. However, in contrast to our hypothesis regarding smoking among patient groups, we found that the patients with schizophrenia who smoke had lower FA in the whole brain, total cortical, frontal and occipital white matter regions in comparison to healthy participants and non-smoking schizophrenic patients. Importantly, we note that these findings were tempered by IQ correction, suggesting that these brain differences may be more related to IQ and not smoking. In addition, we found that within the patient groups (and especially in the smoking group), IQ was positively correlated with FA in multiple regions. However, IQ was not correlated with FA in the control group. Since we unfortunately do not have premorbid measures of IQ, we do not know if the combination of smoking and having schizophrenia adversely impacted the IQ in the smokers in our study.

Numerous DTI studies have demonstrated lower FA in patients with schizophrenia, especially within frontal and temporal white matter, cingulum bundle, and corpus callosum (White et al., 2008). Given the high prevalence of smoking among patients with schizophrenia (74-88%) (reviewed by Dalack et al., 1998), these results likely represented

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patients that were chronic smokers. The findings from this study confirm prior work, since the schizophrenia patients as a group (smoking and non-smoking) had lower FA in total brain, cortical, and frontal white matter regions compared to healthy controls. Further, these results add to a recently published DTI study which reported that schizophrenia and smoking were independent and additive factors in altering FA (Zhang et al., 2010). Using a voxel-wise approach, Zhang and colleagues identified a group effect for FA in the left anterior thalamic radiation, in which patients with schizophrenia who smoke had the lowest FA, significantly lower than smoking controls (but not significantly lower than non-smoking patients). Non-smoking controls had significantly higher FA than all other groups (Zhang et al., 2010). In contrast, in, the results reported here, FA in non-smoking patients did not differ significantly from controls (with or without IQ correction). Methodological differences could in part account for the difference in findings; whereas Zhang et al used a voxel-wise analysis approach to detect white matter differences in localized regions, whereas our approach was to look for global effects in white matter. In addition, Zhang and colleagues did not use IQ as a covariate in their study, which could influence the results. Despite these differences, taken together, the two studies highlight the importance of weighing smoking status as a separate factor when interpreting FA results in schizophrenia research. Our study adds to the prior study by examining the additional impact of IQ, and our results have highlighted the importance of considering this factor in analyses of smoking effects in schizophrenia.

The effects of exposure to cigarette smoking FA in any human population are still in the early stages of research exploration. Interestingly, the two prior studies evaluated FA in otherwise healthy populations that smoke reported *higher* FA in smoking participants compared to controls. In the first study, individuals with both prenatal and adolescent exposure to cigarette smoke had higher FA in anterior cortical white matter, and the adolescent-exposure group also had higher FA in the internal capsule (Jacobsen et al., 2007). In another study, adult smokers had *higher* FA in the corpus callosum compared to controls (although authors noted that smokers with less exposure to cigarette smoke had higher FA compared with smokers with more exposure) (Paul et al., 2008).

Gadzinski and colleagues examined white matter in people with a history of drinking alcohol, with and without a history of smoking (Gazdzinski et al., 2011). This study found no differences in FA, but noted higher mean diffusivity (a measure opposite to FA) in frontal white matter, among nonsmoking drinkers as opposed to smoking drinkers (suggesting more linear organization among smokers than nonsmokers for this drinking population (Gazdzinski et al., 2011). These findings contrast with our findings of *lower* FA values in patients with schizophrenia and suggest the possibility that smoking, or risk for smoking, may impact FA differently across populations.

The notion that smoking impacts neuroimaging findings variably depending on the population has precedent in the structural neuroimaging literature. In one study, although the entire group of patients with schizophrenia had smaller gray matter volumes than controls, smoking patients had *larger* gray matter volumes in lateral prefrontal and superior temporal cortices than non-smoking patients (Tregellas et al., 2007). In contrast, Brody et al. (2004) found that in otherwise healthy adults smokers had *smaller* gray matter volumes in the prefrontal cortex and left dorsal ACC compared to non-smokers (Brody et al., 2004). In support of this second report, a study of individuals that chronically drink alcohol reported that among both light and heavy drinkers, those that smoke had lower total and temporal gray matter volumes than non-smoking drinkers (Durazzo et al., 2007). A number of unknown factors could contribute to the variance across populations in these neuroimaging abnormalities, such as genetic background, comorbidity, degree of exposure to nicotine, and exposure to other, unidentified environmental factors.

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Our detection of significant correlations between IQ and FA in multiple brain regions in both patient groups add to prior DTI studies in various populations that have detected significant relationships between IQ and FA (Schmithorst et al., 2005; Deary et al., 2006; Yung et al., 2007; Chiang et al., 2009; Kontis et al., 2009; Li et al., 2009). A recent twin study reported that FA was under strong genetic control in the frontal, parietal, and occipital lobes, and that common genetic factors mediated the correlation between IQ and FA (Chiang et al., 2009). The other available report on schizophrenia and smoking and white matter did not report IQ or its effects so we are unable to compare findings in that regard. Future advances involving neuroimaging and genetic approaches will be necessary to further tease apart the interaction of effects of smoking and IQ on FA in patients with schizophrenia. Since these results are cross sectional, we can not determine causality; we speculate that individuals who inherit the combined factors of risk for schizophrenia, lower IQ, and disruptions in white matter are more likely to have a severe smoking problem—to smoke more frequently and persistently throughout their lives. Alternatively, it is possible that the combination of smoking and schizophrenia adversely impacts IQ, perhaps via alterations in the white matter pathways in the brain.

There are several limitations to the study. First, we did not have a control group who smoked cigarettes. Such a group would be very valuable to assess whether the effects of smoking interacted with the effects of illness on FA. Notably, in the only other DTI study that has yet reported results on schizophrenia and smoking on white matter (Zhang et al., 2010), a smoking control group was included, and authors reported independent and additive effects for both smoking disease on FA, noting significantly lower FA in the smoking control group compared to the non-smoking control subjects (Zhang et al., 2010). The second limitation is that the study involved two different sites which used different DTI acquisition sequences. This was addressed by transforming the data into z scores to normalize differences across sites and allow for direct comparisons.

The third limitation is that the groups were not IQ matched, an issue that is widespread in schizophrenia research since lower mean IQ of about one standard deviation is commonly observed in groups of patients with chronic schizophrenia (Mesholam-Gately et al., 2009). We addressed this by correcting for IQ in our secondary analyses, which tempered findings. Given that findings were no longer as significant after IQ correction suggests that we must take caution in interpreting the lower FA as a marker specific to smoking, but perhaps as a marker of more severe psychopathology or compromised brain health in that group. We are unaware of previous work demonstrating an association between smoking and IQ in schizophrenia patients, and so our finding that IQ was lower in the smoking group requires additional study. In particular, in the only prior report documenting the impact of smoking on FA in patients with schizophrenia, Zhang and colleagues did not report any information on IQ (Zhang et al.; 2010). We have presented results both with and without correction in order to guide future investigations of white matter and smoking in schizophrenia. Finally, since a small number of the smokers also used a variety of other drugs of abuse, it is possible that these substances influenced the results.

Finally, all studies that examine white matter using diffusion tensor imaging should consider the potential confound of partial volume effects. This is a particularly important issue in schizophrenia research because patients with schizophrenia are known to have accelerated rates of brain atrophy with age in comparison to healthy individuals {DeLisi, 1999 #1223;Schuster, 2011 #1219}. To address this, we estimated an atrophy measure for each person using ROIs that were determined by FreeSurfer (surfer.nmr.mgh.harvard.edu/). The atrophy measure was calculated by subtracting the total brain volume (including cerebellar volume) from the intracranial volume. This calculation essentially yielded a measure of non-brain volume within the skull for each person; a larger volume would suggest a higher level

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of atrophy. An ANCOVA of this atrophy measure controlling for site, sex and age revealed a trend effect for diagnosis (F=3.6, p=0.06); post-hoc least squares means analysis revealed that as expected, patients had more atrophy. (Notably, when IQ was included in the model, the effect of diagnosis on atrophy was no longer significant.) When we repeated the analyses of this study to examine differences related to diagnosis and smoking group and included this estimated atrophy measure as a covariate, the results were largely similar, and in fact the group difference trends after IQ correction became stronger.

In conclusion, we have found preliminary evidence supporting (a) a possible relationship between FA and smoking in patients with schizophrenia, suggesting that smoking status may be an important factor contributing to low FA in schizophrenia studies, and (b) that IQ is an important factor when considering the relationship between smoking and brain white matter in patients with schizophrenia. Questions remain regarding the complex relationships among factors of disease status, smoking, FA, and IQ. Further, it is unknown whether low FA in smoking patients predates illness and potentially represents a biomarker for risk of both developing schizophrenia and for developing nicotine dependence. Future longitudinal investigations in high-risk and early-onset groups are necessary to further investigate the causal pathways that define the complex relationships among the factors of smoking, IQ and FA in schizophrenia.

Abbreviations

(DTI) Diffusion Tensor Imaging

(FA) Fractional Anisotropy

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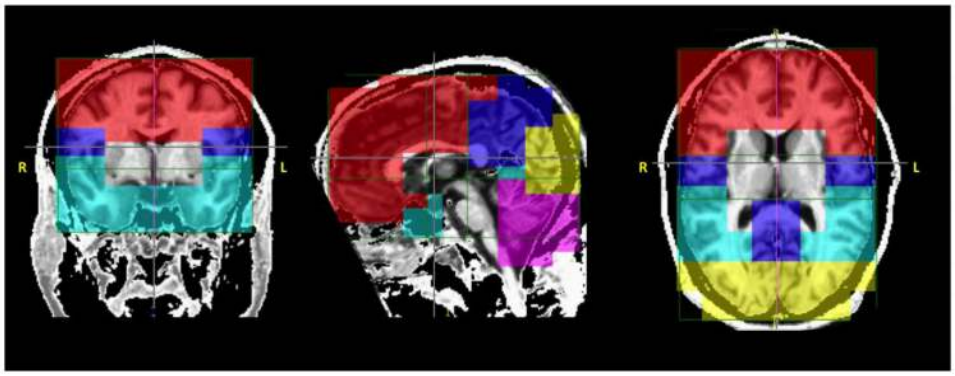

Figure 1.

Illustration of BRAINS2 regions of interest

Color identifiers: red=frontal lobe; blue= parietal lobe; yellow=occipital lobe; purple = cerebellum; turquoise = temporal lobe. The regions are defined within these Talairach boxes as the intersection between segmented white matter and fractional anisotropy greater than 0.1. The whole brain region is defined by all colors. The cortical region is defined by the frontal, temporal, parietal, and occipital lobes.

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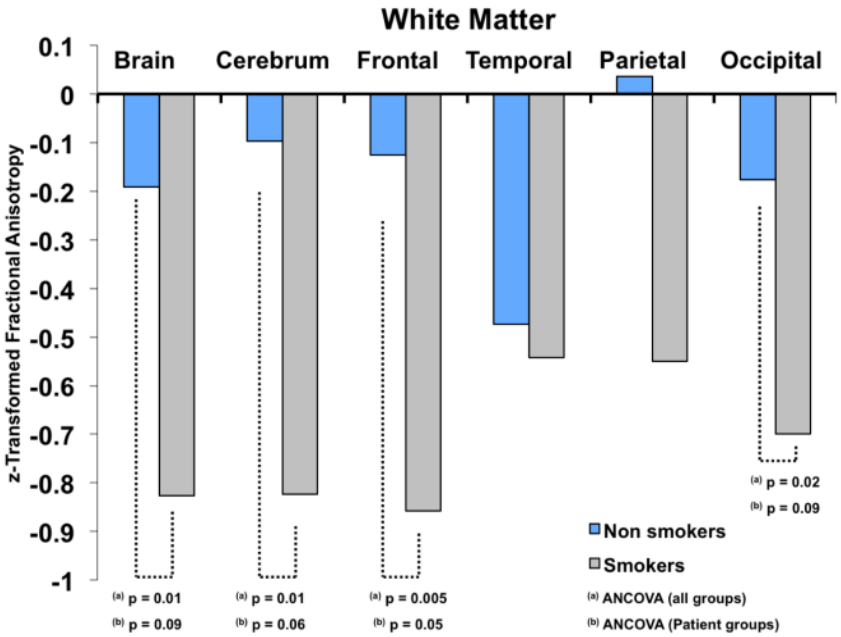

Figure 2.
Comparison of z-transformed FA between groups. Controls are set to zero.

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Table 1

Demographics and Clinical Data for Study Groups

	Smoking Patients (n = 28)	Non-Smoking Patients (n = 15)	Non-Smoking Controls (n = 40)	p
Age (years, SD)	37.7 (10.8)	35.9 (12.8)	31.6 (11.1)	0.07
Sex (M / F)	20 / 8	12 / 3	31 / 9	0.79
Hand (R / L / Both)	24 / 1 / 3	13 / 1 / 1	37 / 2 / 1	0.79
Total estimated IQ	94.2 (14.9)	112.1 (11.4)	113.4 (14.0)	<0.0001 $^{\psi}$
Father's Education	14.5 (3.2)	14.9 (4.3)	14.4 (2.9)	0.36
Mother's Education	12.8 (3.2)	13.9 (4.7)	13.5 (2.6)	0.22

$^{\psi}$Smoking Patients < Non-Smoking Patients = Non-Smoking Controls

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Table 2

Description of Participants by Site[a]

site	group	N	Age	Sex (M/F)	IQ[b]	Mother's Education[c]	Father's Education	Negative symptoms	Positive symptoms	Disorganized symptoms
New Mexico	All New Mexico participants	42	35.8 (13.3)	32/10	105.1 (17.3)	39 (3.5)	35 (3.6)	8.2 (3.2)	4.6 (2.4)	1.8 (1.7)
	Control	18	31.9 (12.9)	15/3	114.0 (15.7)	13.6 (3.1)	14.7 (3.3)	N/A	N/A	N/A
	Schizophrenia, non-smoking	7	44.1 (13.2)	18/3	105.0 (7.5)	10.7 (4.6)	13.1 (4.9)	8.3 (3.0)	3.7 (2.0)	1.6 (2.0)
	Schizophrenia, smoking	17	37.4 (12.7)	7/1	95.1 (17.1)	12.1 (3.2)	13.2 (3.3)	8.2 (3.4)	5.0 (2.5)	1.8 (1.9)
Iowa	All Iowa participants	41	31.4 (9.9)	31/10	108.5 (15.4)	14.2 (2.9)	14.8 (2.9)	8.0 (4.5)	3.7 (2.9)	1.8 (1.7)
	Control	22	31.3 (9.8)	16/6	112.0 (12.7)	13.5 (2.3)	14.2 (2.6)	N/A	N/A	N/A
	Schizophrenia, non-smoking	8	29.0 (7.0)	8/2	119.1 (10.3)	13.5 (2.2)	16.4 (3.2)	9.8 (4.9)	3.7 (2.9)	1.5 (1.3)
	Schizophrenia, smoking	11	33.4 (12.0)	9/2	93.0 (11.54)	13.7 (3.3)	14.7 (3.2)	6.7 (4.0)	3.7 (3.1)	2.1 (2.0)

[a]Means and standard deviations are provided from demographic and clinical variables. IQ was significantly higher in non-smoking patients in Iowa compared to non-smoking patients in Minnesota. Between-site IQ differences were not detected for the other study groups. When grouping all patients together, no site differences between schizophrenia patients were detected for IQ. IQ was significantly higher in non-smoking patients as compared to smoking patients at Iowa, but not at NMex.

[c]Mother's Education was significantly higher at Iowa site: t (78)=2.33, p=0.0233. No other significant differences on clinical or demographic variables were noted between sites.

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Table 3

Clinical Characteristics of Smoking versus Non-smoking Patients with Schizophrenia.

Clinical Measures	Schizophrenia Smokers	Schizophrenia Non-smokers	p
N	26	15	
Years of Illness	12.8 (11.4)	11.7 (10.6)	0.76
Calgary Depression Inventory	3.4 (4.1)	6.0 (5.7)	0.09
AIMS Total	0.14 (0.52)	0 (0)	0.30
Simpson Angus Total	2.5 (4.1)	1.3 (0.6)	0.27
Dose years Antipsychotics	21.3 (30.7)	13.1 (28.7)	0.40
SANS / SAPS Scores			
Positive	4.5 (2.7)	3.7 (2.4)	0.33
Negative	7.6 (3.7)	9.1 (4.0)	0.24
Disorganized	1.9 (1.9)	1.5 (1.6)	0.57

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Table 4

Summary of Brain Fractional Anisotropy Results. Statistics are provided from comparisons between Smoking Patients, Non-Smoking Patients, and Healthy Controls (analyses completed without IQ correction).

Brain Region	z-Score Smoking Patients (Controls set to zero)	z-Score Non-smoking Patients (Controls set to zero)	ANCOVA (3 Groups) $F_{2,79}$ / p	ANCOVA (Patient Smokers vs Non-smokers) $F_{1,47}$ / p	ANCOVA (Patient Non-smokers vs Controls) $F_{1,55}$ / p	ANCOVA (Patient vs Controls) $F_{1,55}$ / p
Total Brain	−0.83	−0.19	4.9 / 0.01	2.0 / 0.16	1.3 / 0.26	6.2 / 0.01
Total Cortical	−0.82	−0.10	4.9 / 0.01	4.7 / 0.04	.44 / .51	5.3 / 0.02
Frontal lobe	−0.86	−0.12	5.6 / 0.005	4.4 / 0.04	0.8 / 0.38	6.2 / 0.01
Occipital lobe	−0.70	−0.18	4.1 / 0.02	2.9 / 0.09	0.33 / 0.56	5.3 / 0.02

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Table 5

Means and standard deviations for FA values of brain regions of interest for each site and each group

White Matter Regions	Iowa			New Mexico		
	Control	Non-smoking schizophrenia	Smoking Schizophrenia	Control	Non-smoking Schizophrenia	Smoking Schizophrenia
Cerebellum	0.263 (0.021)	0.268 (0.016)	0.268 (0.015)	0.245 (0.009)	0.250 (0.023)	0.241 (0.032)
Frontal Lobe	0.319 (0.020)	0.325 (0.019)	0.308 (0.011)	0.302 (0.014)	0.290 (0.027)	0.282 (0.030)
Temporal Lobe	0.302 (0.016)	0.294 (0.017)	0.295 (0.011)	0.248 (0.009)	0.240 (0.014)	0.239 (0.025)
Occipital Lobe	0.250 (0.018)	0.247 (0.008)	0.234 (0.012)	0.192 (0.013)	0.190 (0.015)	0.187 (0.019)
Parietal Lobe	0.333 (0.018)	0.342 (0.020)	0.323 (0.012)	0.294 (0.016)	0.286 (0.012)	0.285 (0.029)
Brain Stem	0.343 (0.024)	0.350 (0.028)	0.346 (0.023)	0.312 (0.020)	0.310 (0.018)	0.308 (0.034)
Total Cortical	0.315 (0.013)	0.319 (0.011)	0.306 (0.009)	0.285 (0.012)	0.277 (0.011)	0.271 (0.026)
Whole Brain	0.310 (0.013)	0.312 (0.010)	0.290 (0.009)	0.259 (0.011)	0.252 (0.012)	0.248 (0.024)