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Abnormal White Matter Connections Between Medial Frontal Regions Predict Symptoms in Patients with First Episode Schizophrenia

Toshiyuki Ohtani^{a,b,h}, Sylvain Bouix^a, Amanda E Lyall^a, Taiga Hosokawa^{a,b,i}, Yukiko Saito^{a,j}, Eric Melonakos^a, Carl-Fredrik Westin^g, Larry J. Seidman^{c,d}, Jill Goldstein^d, Raquelle Meshulam-Gately^c, Tracey Petryshen^{e,f}, Joanne Wojcik^d, and Marek Kubicki^{a,b,*}

^aPsychiatry Neuroimaging Laboratory, Department of Psychiatry, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

^bVA Boston Healthcare System, Boston, MA, USA

^cBeth Israel Deaconess Medical Center-Massachusetts Mental Health Center, Public Psychiatry Division, Harvard Medical School, Boston, MA, USA

^dDepartment of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

^eStanley Center of Psychiatry Research, Broad Institute of MIT and Harvard, Boston, MA, USA

^fPsychiatry and Neurodevelopmental Genetics Unit, Center for Human Genetic Research, Massachusetts General Hospital, Boston, MA, USA

^gSurgical Planning Laboratory, MRI Division, Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

^hSafety and Health Organization, Chiba University, Chiba City, Chiba, Japan

ⁱTsuchida Hospital, Tokyo, Japan

^jDepartment of Neuropsychiatry, Kansai Medical University, Moriguchi City, Osaka, Japan

Abstract

Introduction—The medial orbitofrontal cortex (mOFC) and rostral part of anterior cingulate cortex (rACC) have been suggested to be involved in the neural network of salience and emotional processing, and associated with specific clinical symptoms in schizophrenia. Considering the schizophrenia dysconnectivity hypothesis, the connectivity abnormalities between mOFC and rACC might be associated with clinical characteristics in first episode schizophrenia patients (FESZ).

Corresponding author: Marek Kubicki, M.D., Ph.D., Psychiatry Neuroimaging Laboratory, Department of Psychiatry, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA, kubicki@bwh.harvard.edu, Tel: +1-617-525-6105; Fax: +1-617-525-6150.

Supplementary data

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Conflict of interest

The authors declare no conflict of interest in relation to the present manuscript.

Methods—After parcellating mOFC into the anterior and posterior part, diffusion properties of the mOFC-rACC white matter connections for 21 patients with FESZ and 21 healthy controls (HCs) were examined using stochastic tractography, one of the most effective Diffusion Tensor Imaging methods for examining tracts between adjacent gray matter regions.

Results—Fractional anisotropy (FA) reductions were observed in bilateral posterior, but not anterior mOFC-rACC connections (left: $p < 0.0001$; right: $p < 0.0001$) in FESZ compared to HCs. In addition, reduced FA in the left posterior mOFC-rACC connection was associated with more severe anhedonia-asociality ($\rho = -0.633$, $p = 0.006$) and total score ($\rho = -0.520$, $p = 0.032$) in the Scale for the Assessment of Negative Symptoms (SANS); reduced FA in the right posterior mOFC-rACC connection was associated with more severe affective flattening ($\rho = -0.644$, $p = 0.005$), total score ($\rho = -0.535$, $p = 0.027$) in SANS, hallucinations ($\rho = -0.551$, $p = 0.018$), delusions ($\rho = -0.632$, $p = 0.005$) and total score ($\rho = -0.721$, $p = 0.001$) in the Scale for the Assessment of Positive Symptoms (SAPS) in FESZ.

Conclusions—The observed white matter abnormalities within the connections between mOFC and rACC might be associated with the psychopathology of the early stage of schizophrenia.

Keywords

White matter; Fractional anisotropy; Orbitofrontal cortex; Anterior cingulate cortex; First episode schizophrenia

1. Introduction

Clinically, a majority of patients with early stages of schizophrenia, a population frequently referred to as first episode schizophrenia (FESZ), demonstrate positive symptoms such as hallucinations and delusions. Negative symptoms also exist in the early stage of the illness, although *are observed less frequently in FESZ than in chronic schizophrenia populations*. Aberrant salience has been proposed as an important mechanism in the production of psychotic symptoms such as delusions and hallucinations (Palaniyappan et al., 2011). Inappropriately excessive salience attached to external events is thought to be associated with delusions, while such salience when attached to self-generated responses may contribute to hallucinations (Kapur, 2003). The anterior cingulate cortex (ACC) is a part of the ‘salience network’ (Seeley et al., 2007), and it has been suggested that dysfunction of this network may result in misattribution of salience to ordinarily inconsequential events, which might in turn result in hallucinations and/or delusions (Kapur, 2003). Furthermore, auditory verbal hallucinations are associated with functional abnormalities in the ACC (Allen et al., 2007), and other neuroimaging studies have reported reduced activity in the ACC in schizophrenia patients *exhibiting delusions* (Lahti et al., 2006; Blackwood et al., 2004; Erkwow et al., 1997). Meanwhile, it has been posited that abnormalities in the orbitofrontal cortex (OFC) may be mediating symptom misattribution by conferring aberrant salience to perceived symptomatology (Shad et al., 2006). Of interest, a PET study of schizophrenic patients with hallucinations reported increased activation in the OFC (Silbersweig et al., 1995) which provides further evidence that the OFC might be involved in generating this positive symptom. In addition, delusion misattribution in *patients experiencing the first episode of psychosis was associated with cortical thickness in the*

OFC (Buchs et al., 2012) also providing evidence for the association between delusions and abnormalities in the OFC. These previous studies suggested ACC and OFC to be associated with the psychopathology of hallucinations and delusions.

On the other hand, patients with schizophrenia, starting from the early stage of the illness, also show abnormal emotional responses and an increased difficulty with social interaction, suggestive of abnormal emotional processing. It has been proposed that the OFC and ACC play distinct, but complementary, roles in mediating normal patterns of emotional and social behavior (Rudebeck et al., 2008). Among the OFC sub-regions, the medial OFC (mOFC) is activated by emotional stimuli (for a review see Phan et al., 2002), while the posterior OFC may function as a general significance detector that particularly responds to salient and behaviorally relevant events in the environment (Diekhof et al., 2011). For the ACC sub-regions, the rostral part of ACC (rACC) is the affective sub-region of ACC and is primarily involved in assessing the salience of motivational and emotional information and regulating emotional responses (Allman et al., 2001; Bush et al., 2000). *Previous studies have suggested that close functional relationships exist between the mOFC and rACC (Goldstein et al., 2007; Elliott et al., 2002), as well as between the posterior OFC and the ventral cingulate cortex (Elliott et al., 2002).* Therefore, we focused our analysis on the white matter (WM) properties in the connections between functionally related regions of the mOFC and rACC, in an effort to understand the structural connections underlying the salience network and the pathophysiology of positive and negative symptoms in schizophrenia.

The dysconnectivity hypothesis of schizophrenia proposes that schizophrenia results from poor or mis-wired anatomical connections between distinct brain regions, leading to functional disintegration (Foucher et al., 2005; Konrad and Winterer 2008; Pettersson-Yeo et al., 2011). Postmortem and genetic studies have provided evidence for anatomical dysconnectivity and myelination abnormalities in schizophrenia (Davis et al., 2003; Segal et al., 2007). We hypothesize that the WM connections between the mOFC and the rACC will be abnormal because of the functional cooperation between the mOFC and the rACC in many important cognitive processes along with the association between structural abnormalities in OFC/ACC and emotionally or sociality-related symptoms. We further suggest that these abnormalities might be associated with specific clinical symptoms of schizophrenia, such as hallucinations, delusions, affective flattening, and anhedonia-asociality. To test this hypothesis, we examined the properties of WM connections between mOFC and rACC using Diffusion Tensor Imaging (DTI) Tractography, and explored the relationship between the WM pathology and the clinical symptoms in schizophrenia. In this study, we investigated patients with FESZ. This population is typically younger than most frequently studied chronic schizophrenia populations, and thus free from some of the confounding factors usually associated with the later populations, i.e. changes related to aging, medication, and disease chronicity. *This population provides an avenue to study the relationships between changes in WM and neuropsychopathology associated with disease,* as well as be helpful in establishing a baseline for further studies focusing on disease progression and conversion to psychosis.

DTI has been used for examining microstructural WM properties and is sensitive to WM fiber tract integrity and myelination. It has become the most popular method in examining the connectivity between brain regions in healthy subjects and dysconnectivity in various neuropsychological diseases. Most DTI studies investigating specific WM connections in the brain implement streamline tractography. This popular method estimates tracts by following the direction of maximal water diffusion of the WM voxels.

Among the measures that reflect the WM properties, Fractional Anisotropy (FA) reduction has been reported to occur in response to axon death, myelin damage, damage to the axon membrane, and reduced “fiber coherence” (Kubicki et al., 2007), *and reduced FA is most commonly reported in schizophrenia* (Gasparotti et al., 2009; Zhang et al., 2010; Ohtani et al., 2014). Patients with schizophrenia exhibit abnormalities in integrity of both myelin sheaths as well as axon membranes (Uranova et al., 2007; Davis et al., 2003). *In a study performed in an animal model, Song and colleagues showed that while the damage to the myelin of the optic nerve results in increased Radial Diffusivity (RD) but does not change Axial Diffusivity (AX) (Song et al., 2002), damage to the axonal membrane of the optic nerve with the myelin preserved results in reduced AX but unchanged RD (Song et al., 2003).* Thus, RD is thought to be a putative measure of myelin integrity, and AX is, on the other hand, thought to be a putative measure of axonal integrity.

At present, a number of studies have investigated major WM connections (tract bundles) in schizophrenia (reviewed by Peters et al., 2010). To date DTI studies have produced some evidence for widespread WM abnormalities in FESZ (Gasparotti et al., 2009; Fitzsimmons et al., 2014) and chronic patients (Konrad & Winterer, 2008; Kubicki et al., 2011; Liu et al., 2013), though findings are less consistent in the FESZ. While many studies have examined major WM connections, to our knowledge, no DTI study has investigated the WM projections between the mOFC and the rACC, even though the mOFC and the rACC are anatomically located close to each other, and as we described above, strongly connected functionally. One reason for this may be the limitation of streamline tractography method. Streamline tractography does not provide information regarding the certainty of the estimated fiber tracts. Therefore, uncertainty of the generated tracks caused by increased imaging noise (i.e. diffusion signal within the gray matter) or complex fiber configurations (i.e. fiber crossings) are not taken into account. Thus, streamline tractography is not an optimal tool for studying connectivity between gray matter (GM) regions. The stochastic tractography method (Björnermo et al., 2002) is a Bayesian approach that addresses the described weaknesses of streamline tractography by performing tractography under a probabilistic framework that accounts for uncertainty in the diffusion tensor field. This method uses probabilistic model of imaging noise and fiber architecture to infer the underlying fiber configuration. Since stochastic tractography models uncertainty and does not use any stopping criteria for generating tracts, this method is not limited in generating tracts in *regions with low uncertainty (i.e. low FA)*. Thus, stochastic tractography can track through fiber crossings and be used in gray matter. This makes stochastic tractography a superior method for directly assessing the connectivity of GM with other regions of the brain, and model and measure the anatomy of specific functional networks in the brain (Kubicki et al., 2011). Moreover, as proposed by Kreher et al. (2008), the strength of

anatomical connectivity between two ROIs can also be examined by the certainty of WM connection measured along the tract.

In this study, we used stochastic tractography in order to model the direct connections between the mOFC and the rACC as well as to detect abnormalities in fiber integrity and connectivity between the mOFC and the rACC in FESZ. Since such a model should include both GM regions as well as WM connections, we also measured GM volumes of these regions, and the relationships between GM volumes and WM measurements to confirm the effects of GM volume reduction on the WM properties. In addition, we examined the association between FA in the abnormal mOFC-rACC connections (i.e. connections that showed FA difference between FESZ and HCs) and the specific symptoms such as hallucinations, delusions, emotion-related negative symptoms, and overall positive and negative symptoms severity to examine whether the WM connections between mOFC and rACC can predict psychotic symptoms in FESZ.

2. Methods

2.1. Participants

Twenty-one patients (15 males/6 females) diagnosed with FESZ (*5 with paranoid type, 1 with disorganized type, 5 with schizoaffective disorder, 8 with undifferentiated type schizophrenia, and 2 with schizotypal disorder*) and twenty-one control subjects (15 males/6 females) were recruited as part of the Boston Center for Intervention Development and Applied Research (CIDAR) study. All patients met criteria for a DSM-IV diagnosis of schizophrenia. They ranged in age from 14 to 31 years. *Among the 21 patients, 15 were treated with only atypical antipsychotics, 3 with both of typical and atypical antipsychotics, one with antidepressants and mood stabilizer, and 2 without any medication.* There were no patients with who had longer than one year of continuous antipsychotic treatment, and no patients who had another family member participating in the Boston CIDAR study. Patients were excluded if they had a history of *electroconvulsive therapy* within the past 5 years. Diagnoses were based on a diagnostic interview using the Structured Clinical Interview for the DSM-IV-TR, Research Version (SCID) for ages >18 (First et al., 2002), or the KID-SCID (Hien et al., 1994) for subjects 13–17 years of age.

Control subjects were screened for the presence of an Axis I disorder using the Structured Clinical Interview for DSM-IV-TR, Non-patient Edition (First et al., 2002), and were excluded if they: 1) currently met criteria for any psychosis, major depressive disorder, dysthymic disorder, bipolar disorder, obsessive compulsive disorder, post traumatic stress disorder, dissociative disorders, anorexia nervosa, bulimia nervosa, or developmental disorders, 2) had a history of any psychosis, major depression (recurrent), bipolar disorder, obsessive compulsive disorder, post traumatic stress disorder, developmental disorder, or psychiatry hospitalization, 3) had current or past use of antipsychotics for any psychiatric condition (other past psychotropic medication use acceptable, but must be off medicine for at least 6 months before participating in the study, except for medications like sleeping medications or anxiolytic agents, like beta-blockers for performance anxiety, tremors, etc.), 4) had any history of ECT, 5) had evidence of any prodromal symptoms, or schizotypal or

other Cluster A personality disorders, or 6) reported having a first-degree relative with psychosis. (See Table 1 for demographic information for patients and controls.)

For all subjects exclusion criteria included sensory-motor handicaps, neurological disorders, medical illnesses that significantly affect neurological functioning, diagnosis of mental retardation, education of less than 9th grade (or less than 5th grade for subjects under 18), non-fluency in English (exposure to English by age 6), substance abuse in the past month as defined by the DSM-IV-TR, substance dependence (excluding nicotine) in the past 3 months as defined by the DSM-IV-TR, and current suicidality. For their safety during the MRI scanning, all subjects were screened for foreign metal in their body, pacemakers, pregnancy, claustrophobia, or any other circumstance that might pose a health risk. Written informed consent was obtained for all subjects, as well as parental/legal guardian consent for subjects under the age of 18. The patients were either not medicated (three patients) or medicated with typical and/or atypical antipsychotic medication (eighteen patients). All medication dosages were converted to chlorpromazine equivalents (Woods, 2003). In order to evaluate positive symptoms and negative symptoms in schizophrenic patients, the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984), and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1981) were administered. The contents of SANS items for “Affective Flattening or Blunting”, “Anhedonia-asociality”, and total score of SANS, and the contents of SAPS items for “Hallucinations”, “Delusions”, and total score of SAPS were described in the online supplemental materials. We used the sum of the actual individual ratings for analyses. SAPS, SANS, and neuropsychological evaluation was performed at protocol entrance, with MRI scans occurring no more than one week later. This study was approved by the local IRB committees at Beth Israel Deaconess Medical Center, the Veterans Affairs Boston Healthcare System (Brockton campus), Harvard Medical School, and Brigham and Women’s Hospital.

2.2 MRI Protocol

The detail of MRI protocol was described at supplemental methods (online supplemental materials).

DTI data was collected on the 3 Tesla GE Echospeed system (General Electric Medical Systems, Milwaukee, WI). Scans were acquired with echo planar imaging (EPI) DTI Tensor sequence, and a double echo option to reduce eddy-current related distortions (Heid, 2000; Alexander, 1997). To reduce impact of EPI spatial distortion, an 8 Channel coil and ASSETT (Array Spatial Sensitivity Encoding techniques, GE) with a SENSE-factor (speed-up) of 2 was used. Product GE sequence has been modified in order to accommodate for higher spatial resolution required by this study. Eighty-five axial slices parallel to the AC-PC line covering whole brain were acquired, in 51 diffusion directions with $b=900$. In addition 8 baseline scans with $b=0$ were also acquired. Scan parameters were as follows: TR 17000ms, TE 78ms, FOV 24cm, 144×144 encoding steps, 1.7mm slice thickness, producing isotropic $1.7 \times 1.7 \times 1.7$ mm voxels. In addition to DTI scans, structural MRI acquisition protocol was also used, which includes two MRI pulse sequences. The first results in contiguous spoiled gradient-recalled acquisition (fast SPGR) with the following parameters; TR=7.4ms, TE=3ms, TI=600, 10 degree flip angle, 25.6cm^2 field of view, matrix =

256×256. The voxel dimensions are 1×1×1 mm. The second- XETA (e Xtended Echo Train Acquisition) produces a series of contiguous T2-weighted images (TR=2500ms, TE=80ms, 25.6cm² field of view). Voxel dimensions are also 1×1×1 mm. This latter sequence is used as the additional channel of information for brain segmentation and between-modalities registration.

2.3 Image Processing

The explanation for the region of interest (ROI) creation and stochastic tractography generation are described in the online supplemental materials in detail. The ROIs and stochastic cloud are displayed in Fig. 1.

2.4 Data Analysis

In the comparisons between FESZ and healthy control (HC) groups for the demographic variables such as age, handedness, parental and subject's own socioeconomic status (SES), and WRAT 4 Reading Scaled scores, two-tailed independent t-tests were performed considering equal variance. Relative volumes for the regions of interest (ROI) (absolute volumes corrected for the whole brain volumes) as well as measures of anatomical connectivity between these regions were extracted and subjected to quantitative analysis. Data were analyzed using the Statistical Package for Social Sciences (SPSS v.19.0). At first, relative volumes of the ROIs were analyzed with the analysis of variance (ANOVA) using two within-factors of region (three levels: ant mOFC, post mOFC and rACC) and hemisphere (two levels: left and right) and one between-factor of group (FESZ and HCs). Interactions were followed with the separate repeated measures ANOVAs for the ROI with hemisphere as a within factor and a between factor of group. Finally, the interaction with ROI was pursued with a one-way ANOVA, and the cut-off point of significance was set as $p < 0.00833$ after applying Bonferroni's correction. Then, mean FA, RD, AD, and Trace in the four connections were analyzed using ANOVA with two within-factors of connection (two levels: ant mOFC-rACC, and post mOFC-rACC) and hemisphere, and one between-factor of group. Interactions were followed with the separate ANOVA for the connection between ant mOFC-rACC and post mOFC-rACC with side as a within-factor and group as a between-factor. Finally, the interaction with connection was pursued with a one-way ANOVA, and the cut-off point of significance was set as $p < 0.0125$ after applying Bonferroni's correction. *In addition, we also performed analysis of covariate (ANCOVA) setting age as a covariate to explore the effect of age on the observed results.* A Greenhouse-Geisser correction was used to report p-values for all interactions where sphericity could not be assumed. At last, the correlations between the relative volumes of the ROIs and the mean FA, RD, AD, and Trace values of the tracts generated from the ROIs were examined by Spearman's rank-order correlation in order to confirm the effect of volume on the results of these WM variables.

FA is thought to reflect various aspects of WM properties including fiber density, axonal diameter, and myelination (Mori et al., 2005; Oishi et al., 2009). Many previous studies have examined the association between WM abnormalities and behavior as well as the psychopathology of mental disorders. FA, even though not as specific to microstructural pathologies as other diffusion indices (Song et al., 2002; 2003), is still regarded as the most

reliable measure for examining the association between physiology and psychological or clinical characteristics in mental disorders (Duda et al., 2010; Liu et al., 2010; Cui et al., 2011). We thus examined the associations of the mean FA values for specific connections that show abnormality in the group comparison, with the specific symptoms in SAPS and SANS scores for the schizophrenia group using Spearman's rank-order correlation. *The resulting p-values were corrected for the number of connections that show FA abnormality in the group comparison.* Furthermore, we examined the association between the relative volumes of the ROIs and the SAPS and SANS scores to confirm the effect of volume change on the scores of SAPS and SANS.

2.5. Medication

Daily chlorpromazine equivalent antipsychotic dosage (Woods, 2003) was 538.4 ± 511.2 mg, and the content of the medication was as follows: typical antipsychotic, 19.0%, atypical antipsychotic, 85.7%, both, 19.0%, and unmedicated at the scan time, 14.3%. The antipsychotic dosage did not correlate with the mean value of FA, RD, AX, and Trace for any of the four examined connections (left ant mOFC-left rACC, right ant mOFC-left rACC, left post mOFC-left rACC, and right post mOFC-right rACC).

3. Results

Repeated measures ANOVAs revealed no significant between-group differences in mOFC and rACC relative volumes ($F[1,40]=1.127$, $p=0.295$).

Fig. 2 shows the scatter plots for FA across the four connections for the FESZ and healthy control groups. Repeated measures ANOVAs revealed significant between-group differences in FA ($F[1,40]=38.380$, $p<0.0001$) and significant interactions between group and hemisphere ($F[1,40]=11.338$, $p=0.002$), and between hemisphere and connection ($F[1,40]=4.482$, $p=0.041$). *The analysis using ANCOVA also revealed significant group differences in FA ($F[1,39]=36.205$, $p<0.0001$) and significant interactions between group and hemisphere ($F[1,39]=9.398$, $p=0.004$) showing that the significance in group differences and interactions between group and hemisphere remains after controlling for the effects of age.* Post hoc analysis revealed significant differences in bilateral posterior mOFC-rACC connections (left: $F[1,40]=25.384$, $p<0.0001$; right: $F[1,40]=34.159$, $p<0.0001$), however, the connection between bilateral anterior mOFC-rACC did not reach statistical significance (left: $F[1,40]=5.917$, $p=0.020$; right: $F[1,40]=5.382$, $p=0.026$) after applying Bonferroni's correction (Table 2). Comparisons between FESZ group and HC group for the RD, AD, and Trace are shown in Table 2. The FESZ group showed significant mean FA reduction in bilateral posterior mOFC-rACC connections; mean RD increase in bilateral anterior mOFC-rACC connections and bilateral posterior mOFC – rACC connections; and mean Trace increase in right anterior mOFC-rACC and right posterior mOFC – rACC connections.

No significant association could be observed between the ROIs' relative volume and mean FA, AD, and Trace in the tracts that connect the ROIs, suggesting that gray matter volumes in the ROIs and WM integrity might be independent of each other. In addition, no association could be found between the duration or the dosage of medication and mean FA,

RD, AD, and Trace values in the four connections between mOFC and rACC. Furthermore, no significant difference was found between typical and atypical antipsychotic medication for the mean FA, RD, AD, and Trace values.

Since the number of connections that showed group differences in FA was two, we reported the correlations whose p values were less than 0.025 for the correlation analysis. In the FESZ, mean FA reductions in left posterior mOFC-rACC connection were associated with the sum of item scores in anhedonia-asociality ($\rho=-0.633$, $p=0.006$, $n=17$); and right posterior mOFC-rACC connection FA was associated with the sum of item scores in affective flattening ($\rho=-0.644$, $p=0.005$, $n=17$) in the SANS, delusions ($\rho=-0.632$, $p=0.005$, $n=18$), and total score ($\rho=-0.721$, $p=0.001$, $n=18$) in the SAPS (Fig. 3). Although not significant after corrections for multiple comparisons, the left posterior mOFC-rACC connection FA showed a relatively weak association with total score of SANS ($\rho=-0.520$, $p=0.032$, $n=17$). Similarly, the right posterior mOFC-rACC connection FA showed relatively weak association with total score of SANS ($\rho=-0.535$, $p=0.027$, $n=17$) and the sum of item scores in hallucinations ($\rho=-0.551$, $p=0.018$, $n=18$) in the SAPS. No association could be found between the ROIs' relative gray matter volumes and the scores of SAPS and SANS in schizophrenia.

4. Discussion

Using stochastic tractography, we examined the WM properties of bilateral mOFC-rACC connections. The primary finding of this study was of FA, RD, and Trace abnormalities in mOFC-rACC connections in patients with FESZ. The ROI gray matter volumes (i.e. bilateral anterior mOFC, posterior mOFC, and rACC) showed no significant reduction in the FESZ population. Additionally, no associations were found between the ROI gray matter volumes and WM values such as FA, RD, AD and Trace for any of the tracts. This might suggest that the ROI gray matter volumes may have little or no effect on the results of the WM comparison, further indicating that GM and WM pathologies might not be related to each other in the early stages of schizophrenia. The second finding of this study were the associations between FA reductions and severity of clinical symptoms. Specifically, the FA reductions in the left posterior mOFC-rACC connection were associated with more severe anhedonia-asociality on the SANS. In addition, the FA in the right posterior mOFC-rACC connections was associated with more severe affective flattening on the SANS; delusions and overall positive symptoms scores on the SAPS, although the association with hallucinations on the SAPS was relatively weak ($p=0.018$). Accordingly, and consistent with our hypothesis, the observed FA reductions in bilateral posterior mOFC-rACC connections were associated with severity of clinical pathology (specifically delusions and emotional related negative symptoms) in FESZ.

4.1. WM abnormality in FESZ

To date widespread WM abnormalities in FESZ have been reported in several publications (Hao et al., 2006; Federspiel et al., 2006; Price et al., 2007; Szeszko et al., 2008; Cheung et al., 2008; Karlsgodt et al., 2008; Gasparotti et al., 2009; Pérez-Iglesias et al., 2010; Peters et al., 2009a; Peters et al., 2009b; Kawashima et al., 2009; Dekker et al., 2010). Our results are consistent with these previous studies by showing WM abnormality in FESZ. Furthermore,

abnormally increased RD without changes in AD, which *were* observed in FESZ compared to HCs in the bilateral anterior mOFC-rACC connection and the posterior mOFC-rACC connections, suggest that the abnormalities in the fibers of these connections were more likely underpinned by myelin abnormalities as opposed to axonal damage. Since Trace is the sum of the total diffusivity and reflects both the RD and AD, the observed Trace increase might reflect significant RD increase even though the AD change was not significant. If the observed diffusion abnormalities in the fibers between the mOFC and the rACC were indeed the result of myelin *abnormalities* (i.e. “*dysmyelination*”), this might be expected to result in slowed impulse conduction (Roy et al., 2007) and affect various brain functions. Patients with schizophrenia with the most profound diffusion abnormalities may show the most severe conduction delays and therefore, would exhibit the most severe psychopathology (Whitford et al., 2010). Thus, the observed association between FA reduction and more severe clinical symptoms in patients with schizophrenia might reflect the abnormality in WM fiber connections that might be caused by conduction delays.

4.2. Effects of Medication

No significant association was found between the duration or medication dosage and the WM variables. The type of antipsychotic medication also did not affect DTI measures. Previous studies examining effects of antipsychotic medication on DTI measures found no differences between chronically and briefly medicated patients (Kanaan et al., 2009), and no significant correlations between FA and the duration or the dose of antipsychotic medication (Peters et al., 2008; Peters et al., 2009). In addition, the studies in antipsychotic drug-naïve FESZ patients are of particular interest, showing FA reductions not attributable to antipsychotic medication (Cheung et al., 2008; Zou et al., 2008; Gasparotti et al., 2009). These studies suggested that WM abnormalities in FESZ might be independent of the medication effects, and our results are consistent with these studies.

4.3. WM Abnormality and Symptom Severity

Our results are consistent with the results of many previous studies showing negative correlations between FA and psychotic symptom severity. Those correlations were reported for several white matter structures, including corpus callosum (Hubl et al., 2004; Rotarska-Jagiela et al., 2008), cingulum bundle (Hubl et al., 2004), arcuate fasciculus (Hubl et al., 2004), superior longitudinal fasciculus (Soek et al., 2007), and inferior fronto-occipital fasciculus (Szeszko et al., 2008), all of which exhibited that more profound the diffusion abnormalities, the greater the symptom severity in schizophrenia. *However*, several studies reported correlations *contradictory to our findings*. *These studies found* positive correlations between FA and positive symptoms (Karlsgodt et al., 2008; Szeszko et al., 2008) *in the* early stage of schizophrenia. *The conflicting results may be caused by a number of differences between these studies and ours, including differences in the ROIs, image acquisition protocols and post-processing methods, and differences in the demographics of the study populations.* Further studies controlling for the subjects’ age and the stage of schizophrenia might reveal region specific abnormalities and the association with the symptoms according to the stage of the illness.

4.4. WM Abnormalities and Positive Symptoms

In the present results, the FA reduction in the WM between the right posterior mOFC and the right rACC was *significantly* associated with severity of delusions and overall positive symptom severity, while the association with severity of hallucinations was at the trend level. *Within the salience network, the ACC and OFC have been identified as specialized nodes for sympathetic efference and interoceptive feedback* (Critchley, 2005; Critchley et al., 2004), *and dysfunction of this network might lead to misattribution of salience to ordinarily inconsequential events, which might in turn result in hallucinations and/or delusions* (Kapur, 2003). Previous studies demonstrated that schizophrenia patients *with delusions* showed abnormal activation in ACC (Blackwood et al., 2004). Additionally, the OFC has previously been shown to play a selective role in delusion misattribution in first episode psychosis (Buchs et al., 2012). Studies have also suggested an association between abnormal activation in the right ACC and auditory hallucinations (Silbersweig et al., 1995; Brüne et al., 2008), whereas abnormal *[18F]-fluorodeoxyglucose* metabolism *in the ACC* has been also suggested to be associated with hallucinations' severity (Cleghorn et al., 1992). In addition, the right orbitofrontal region shows abnormal activation during auditory verbal hallucinations in patients with FESZ (Parellada et al., 2008). Although the association between hallucinations and white matter integrity in our study is relatively weak, our results stay consistent with these previous studies further suggesting a possible association between abnormalities in the WM anatomical connectivity and functional deficits *observed* in patients with hallucinations. As for the laterality of the WM abnormalities and symptom severity associations, previous DTI studies have reported that lower anisotropy in the tracts of the right hemisphere was associated with more prominent positive symptoms (Mitelman et al., 2007) and that FA reduction in the right anterior cingulum showed trend-level association with more severe positive symptoms (Tang et al., 2010). Therefore, our results are consistent with these previous studies.

4.5. WM Abnormalities and Negative Symptoms

FA reductions of the WM in the left posterior mOFC-rACC connections seem to be associated with the severity of anhedonia-asociality, while those in the right posterior mOFC-rACC connections are associated with severity of affective flattening. While the mOFC shows activation when emotional stimuli are presented in fMRI experiments (for a review see Phan et al., 2002), the rACC is primarily involved in assessing the salience of emotional information and regulating emotional responses (Allman et al., 2001; Bush et al., 2000). Thus, the connection between the OFC and the ACC likely plays a role in emotional processing (de Marco et al., 2006). Accordingly, the abnormal connectivity between the OFC and the ACC might result in deficits in emotional processing that lead to patients with schizophrenia developing affective flattening and anhedonia. On the other hand, the OFC and ACC were previously associated with social cognition (Hughes & Beer, 2011). Moreover, previous neuroimaging studies have examined brain function during tasks regarding Theory of Mind (ToM), which showed heightened OFC activation during the task (Baron-Cohen et al., 1994; Brunet et al., 2000). Lesions in the OFC have been associated with disturbances in social and emotional judgment and behavior (Berlin et al., 2004) suggesting the importance of the OFC in social interaction. ACC activation during an

empathy condition suggests the importance of the ACC in processing empathy-provoking stimuli (Völlm et al., 2006). In addition, Walter et al. (2004) suggests that the paracingulate area is important in social interaction. The observed dysconnectivity between the posterior mOFC and the rACC may affect normal communication between the OFC and the ACC that are necessary for social behavior and interaction and might ultimately lead to asociality. For the laterality of the observed associations, present results are somewhat inconsistent with previous study suggesting left hemisphere impairment associated with negative symptoms (Caligiuri et al., 2005). The demographics of our subjects (i.e. the stage of illness, medication history, age, gender, and handedness), ROI placement, and the clinical profile of patients might all affect the results. However, it is still unclear as to why abnormalities in left posterior mOFC-rACC connection were associated with the severity of anhedonia-asociality and that in right posterior mOFC-rACC connection were associated with the severity of affective flattening, as to our knowledge, no study reported previously relationship between the laterality of WM abnormality in mOFC-rACC connections and specific negative symptoms. Further studies are needed to examine role of white matter laterality in schizophrenia psychopathology.

Observed abnormalities in bilateral anterior and posterior mOFC-rACC connections, and the association between the degree of posterior mOFC-ACC dysconnectivity and the positive/negative symptom severity supports our hypothesis that WM connections between the mOFC and the rACC might be abnormal, and that these abnormalities may be associated with specific symptoms of FESZ. Further studies examining the associations between WM fiber connectivity and the functional connectivity between OFC and ACC, along with their clinical correlates in FESZ might reveal the role of this pathway in the pathology of the early stage of schizophrenia.

4.6. Limitations

First, eighteen out of 21 patients were medicated; however, we found no correlation between medication (chlorpromazine equivalents) and FA, RD, AD or Trace. Second, *we only performed correlation analysis between the symptoms severity and FA in the connections that showed abnormal FA and corrected the p-values by the number of those connections. Therefore, we reported the correlations whose p-values were less than 0.025, since the number of connections that showed abnormal FA was two. We did not use Bonferroni correction for the correlation analysis, since we feel that Bonferroni correction would be too stringent in this case, even though some of our correlations were relatively strong (p-values of several correlation analysis were 0.005 or 0,006). Furthermore, since, the aim of this study was to examine the validity of our hypothesis about the association between WM properties in the mOFC-rACC connections and specific clinical symptoms in FESZ, the observed results were hypothesis driven.*

5. Conclusion

The main findings of this study were of FA reductions as well as significant increases in RD and Trace without significant AD change in fibers between the mOFC and the rACC, suggesting that dysmyelination might affect normal connectivity in this region in patients with FESZ. In addition, FA reduction in the fibers connecting the posterior mOFC and

rACC was related to severity of delusions and emotion related negative symptoms in FESZ implying an association between the posterior mOFC-rACC dysconnectivity and psychopathology of the early stage of schizophrenia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Fig. 1.

a) The stochastic cloud connecting the medial orbitofrontal cortex (mOFC) and the rostral anterior cingulate cortex (rACC). The light green structure is stochastic cloud, the orange is anterior part of mOFC, red is posterior part of mOFC, and the purple is the rACC. b) The model of connection between anterior mOFC and rACC. The light green part is the region connecting anterior part of mOFC and rACC. c) The model of connection between posterior mOFC and rACC. The light green part is the region connecting posterior part of mOFC and rACC.

Fig. 2. Scatter plots of mean FA, Trace, Axial Diffusivity, and Radial Diffusivity for schizophrenia and the healthy control group. Abbreviations: FA = fractional anisotropy; OFC = orbitofrontal cortex; ACC = anterior cingulate cortex; SZ = schizophrenia group; HC = healthy control group. * $p < 0.0125$, ** $p = 0.001$, † $p < 0.001$. Note that Figure 2 is continued on a second image.

Fig. 3.

Correlations between the mean fractional anisotropy (FA) and clinical symptoms. In the first episode schizophrenia group, smaller FA between the left posterior medial orbitofrontal cortex (mOFC) and the left rostral anterior cingulate cortex (rACC) are associated with more severe anhedonia-asociality symptoms in Scale for the Assessment of Negative Symptoms (SANS); smaller FA between the right posterior medial orbitofrontal cortex (mOFC) and the left rostral anterior cingulate cortex (rACC) are associated with more severe affective flattening symptoms in SANS and delusion symptoms in the Scale for the Assessment of Positive Symptoms (SAPS), and total score of SAPS.

Table 1

Demographic and clinical characteristics of study groups

Variable	Mean (SD)		Independent t test		
	FESZ group (n = 21)	HC group (n = 21)	d.f.	t	P
Age (year)	21.19 (4.81)	22.71 (3.21)	40	1.207	0.235
Handedness ^{a)}	1.00(0.00)	0.90(0.18)	20	2.611	0.017
Socioeconomic status ^{b)}					
Subject's own	2.36 (1.63)	2.08 (0.86)	14.618	0.525	0.608
Parental	2.48 (1.37)	1.95 (0.81)	32.411	1.515	0.139
Education (school year)	13.33 (2.87)	14.10 (1.60)	31.361	1.062	0.296
WRAT-4 reading ^{c)}	111.90 (17.74)	111.73 (15.86)	30	0.028	0.978
Age at symptom onset (years old)	20.07 (4.62) ^{d)}	NA			
Antipsychotic medication dosage ^{e)}	393.28 (309.82)	NA			

Abbreviation: FESZ, first episode schizophrenia; HC, healthy control; WRAT-III: Wide Range Achievement Test 3rd Edition (Gladsjo et al, 1999); NA: data not applicable.

^{a)} Handedness was evaluated using the Edinburgh inventory (Oldfield, 1971) and right-handedness is above zero.

^{b)} Each subject's personal socioeconomic status and parental socioeconomic status was measured by the Hollingshead two-factor index (1 = best, 5 = poorest) (Hollingshead, 1965), which consists of educational and occupational scores.

^{c)} Premorbid intelligence was estimated by the WRAT-III, a reading subtest that measures recognition and pronunciation of printed words, and which is considered to be a good estimate of premorbid IQ (Gladsjo et al, 1999).

^{d)} n = 21.

^{e)} Chlorpromazine equivalent (mg).

Table 2

Mean fractional anisotropy, mode, trace, axial diffusivity and radial diffusivity in the first episode schizophrenia (FESZ) and healthy control (HC) groups

Connection	Hemisphere	FESZ group (n = 21)		HC group (n = 21)		1-factor ANOVA	
		Mean	SD	Mean	SD	F _{1,40}	P
Mean Fractional Anisotropy ^{a)}							
Anterior mOFC – rACC	Left	0.372	0.047	0.405	0.042	5.917	0.020
	Right	0.351	0.031	0.387	0.066	5.382	0.026
Posterior mOFC – rACC	Left	0.340	0.046	0.423	0.062	25.384	<0.001* <i>e</i>)
	Right	0.337	0.061	0.431	0.043	34.159	<0.001* <i>e</i>)
Mean Radial Diffusivity ^{b)}							
Anterior mOFC – rACC	Left	0.000783	0.000087	0.000706	0.000100	7.044	0.011* <i>e</i>)
	Right	0.000747	0.000065	0.000672	0.000070	13.142	0.001* <i>e</i>)
Posterior mOFC – rACC	Left	0.000844	0.000115	0.000714	0.000077	18.349	<0.001* <i>e</i>)
	Right	0.000804	0.000087	0.000667	0.000058	35.833	<0.001* <i>e</i>)
Mean Axial Diffusivity ^{c)}							
Anterior mOFC – rACC	Left	0.00140	0.00018	0.00135	0.00016	1.131	0.294
	Right	0.00131	0.00015	0.00124	0.00015	2.660	0.111
Posterior mOFC – rACC	Left	0.00142	0.000033	0.00141	0.00014	0.059	0.810
	Right	0.00137	0.00016	0.00133	0.00011	0.706	0.406
Mean Trace ^{d)}							
Anterior mOFC – rACC	Left	0.00297	0.00031	0.00276	0.00034	4.347	0.044
	Right	0.00281	0.00027	0.00258	0.00024	8.486	0.006
Posterior mOFC – rACC	Left	0.00311	0.00054	0.00283	0.00023	4.706	0.036
	Right	0.00298	0.00028	0.00267	0.00020	16.955	<0.001* <i>e</i>)

Abbreviations: ANOVA, analysis of variance; SZ, schizophrenia; HC, healthy control; OFC, orbitofrontal cortex; ACC, anterior cingulate cortex; mOFC, rostral part of anterior cingulate cortex; rACC

^{a)} Repeated-measures ANOVA of mean FA with group (FESZ and HC) as the between-subjects factor, and side (left and right) and connection (anterior mOFC – rACC and posterior mOFC – rACC) as the within-subjects factors, and the scan setting as a covariate revealed a main effect for group ($F(1, 40) = 38.380$; $P < 0.0001$). There were significant two way interactions for group×side ($F(1, 40) = 11.338$, $P = 0.002$), and side×connection ($F(1, 40) = 4.482$, $P = 0.041$).

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^{b)} Repeated-measures ANOVA of mean Radial Diffusivity with group as the between-subjects factor, and side and connection as the within-subjects factors, and the scan setting as a covariate revealed a main effect for group ($F [1, 40] = 32.804$; $P < 0.0001$), connection ($F [1, 40] = 4.304$; $P = 0.045$), and side ($F [1, 40] = 5.514$; $P = 0.024$). There was a significant two way interactions for group $\times$ connection ($F [1, 40] = 5.375$, $P = 0.026$).

^{c)} Repeated-measures ANOVA of mean Axial Diffusivity with group as the between-subjects factor, and side and connection as the within-subjects factors, and the scan setting as a covariate revealed a main effect for side ($F [1, 40] = 6.777$; $P = 0.013$), however, no other significant main effect or interaction was found.

^{d)} Repeated-measures ANOVA of mean Trace with group as the between-subjects factor, and side and connection as the within-subjects factors, and the scan setting as a covariate revealed a main effect for group ($F [1, 40] = 15.183$; $P < 0.0001$) and side ($F [1, 40] = 8.647$; $P = 0.005$). There was a significant two way interactions for side $\times$ scan setting ($F [1, 40] = 12.936$, $P = 0.001$).

^{e)} * Statistically significant after corrected by Bonferroni's correction.