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Abnormalities in white matter connections between orbitofrontal cortex and anterior cingulate cortex and their associations with negative symptoms in Schizophrenia: A DTI Study

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Abstract

Introduction—The medial orbitofrontal cortex (mOFC) and rostral part of the anterior cingulate cortex (rACC) are brain regions that are important in the neural network involving emotional processing and decision making, as well as playing an important role in social behavior and interaction. Considering the schizophrenia dysconnectivity hypothesis, observed abnormalities in emotional response and social behavior in schizophrenia might be associated with connectivity abnormalities between mOFC and rACC.

Methods—Twenty-seven patients with chronic schizophrenia and 26 healthy controls were examined using Diffusion Tensor Imaging (DTI). White matter properties in bilateral mOFC-rACC connections were examined using stochastic tractography, which has been shown to be among the most effective DTI methods for examining tracts between adjacent gray matter regions.

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Conflict of interest

This research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Contributors

Dr. Ohtani ran the statistical analyses and wrote the first draft of the manuscript. Dr. Kubicki designed the study, supervised the methodology of stochastic tractography and the content of the manuscript. Sylvain Bouix established the stochastic tractography methodology in this study. Taiga Hosokawa and Yukiko Saito helped with the analyses of stochastic clouds. Ryan Eckbo, Thomas Ballinger, Andrew Rausch and Eric Melonakos ran the pipeline of the stochastic tractography and created the figure of ROIs and stochastic clouds. Dr. McCarley advised the content of the manuscript. Dr. Shenton helped with editing of the manuscript and assisted with methodological questions regarding study design. All authors contributed to and have approved the final manuscript.

Results—Reductions in fractional anisotropy (FA) were observed in left anterior mOFC-rACC connections ($p<0.0001$), and bilateral posterior mOFC-rACC connections (left: $p<0.0001$; right: $p<0.0001$) in patients compared to controls. In addition, reduced FA in left posterior mOFC-rACC connections were associated with more severe anhedonia-asociality ($R=-0.396$, $P=0.041$) and avolition-apathy ($R=-0.426$, $p=0.027$) using the Scale for the Assessment of Negative Symptoms.

Discussion—White matter abnormalities within connections between mOFC and rACC are associated with more severe anhedonia-asociality and avolition-apathy, which suggest that these brain regions may be important in understanding abnormal emotional responses and social behavior in patients with schizophrenia.

Keywords

Diffusion Tensor Imaging; Stochastic Tractography; Orbitofrontal Cortex; Anterior Cingulate Cortex; Schizophrenia

1. INTRODUCTION

Schizophrenia is a mental disease involving abnormal emotional responses and difficulty with social interactions. Clinically, patients with chronic schizophrenia often show lack of motivation and difficulty with decision-making. The orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC) are thought to interact, together, to form a network involved in emotional processing (e.g., de Marco et al., 2006), decision-making (e.g., Krain, et al., 2006; Paulmann et al., 2010), and mediating emotion and social behavior (e.g., Rudebeck et al., 2006). The OFC receives input from various sensory modalities (e.g., Kringelbach and Rolls, 2004) and projects to and from brain structures involved in emotion processing (e.g., Paulmann et al., 2010). Regional specificity within the OFC further suggests that medial OFC (mOFC) is activated by emotional stimuli (see Phan et al., 2002), while posterior OFC makes contributions to motivational processes (e.g., Szatkowska et al., 2011), and may be important for responding to salient, behaviorally relevant events (e.g., Diekhof et al., 2011).

Previous studies suggest a close functional relationship between OFC and the rostral part of ACC (rACC) (Woodward et al., 2006), as well as mOFC and rACC (Elliott et al., 2002) and posterior OFC and ventral cingulate cortex (Elliott et al., 2002). Anatomically, OFC is located in prefrontal cortex and is comprised of Brodmann areas (BA) 10, 11, and the medial part of area 47 (Kringelbach, 2005). The rACC is located anterior to the genu, and includes BA 32 and inferior parts of BA 24 (Vogt et al., 1995). While ACC plays a role in rational cognitive functions, such as reward anticipation, decision-making, empathy and emotion (Decety and Jackson, 2004; Jackson et al., 2006), rACC is the affective subregion of ACC (Bush et al., 2000) 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).

In social communications, self-related processing in the emotional domain (Phan et al., 2004) suggests involvement of medial cortical regions (including mOFC and rACC), referred to as “cortical midline structures” (CMS; Northoff and Bermpohl, 2004). The self

represents crucial points in many psychological and sociological processes, and forms the origin and ultimate starting point of any social interaction (Walter et al., 2006).

The dysconnectivity hypothesis suggests that schizophrenia symptoms are related to aberrant connectivity between distinct brain regions (Konard and Winterer, 2008; Pettersson-Yeo et al., 2011). This hypothesis proposes that schizophrenia results from poor or abnormal anatomical connections, leading to functional disintegration (Foucher et al., 2005). Similarly, postmortem and genetic studies provide evidence for aberrant connectivity, demonstrating myelination abnormalities in schizophrenia (Davis et al., 2003; Segal et al., 2007). Considering the functional cooperation between the mOFC and the rACC in many important cognitive processes, including mediation in emotion and behavior, we hypothesize that the white matter (WM) connections between the mOFC and the rACC might be abnormal in schizophrenia. We hypothesize that these abnormalities might be associated with negative symptoms associated with defective emotional processing and social behavior. To test this hypothesis, we examined WM connections between mOFC and rACC using Diffusion Tensor Imaging (DTI) Tractography, and their association with WM pathology and negative symptoms.

DTI has been used to examine WM properties, and is sensitive to WM fiber coherence, density and myelination. This popular method estimates tracts by following the direction of maximal water diffusion of WM voxels (Mori et al., 2005). A number of studies, to date, have investigated major WM connections (tract bundles) in schizophrenia (reviewed by Kubicki et al., 2007). Among the measures that reflect 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). While damage to myelin of 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 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, while AX is thought to be a putative measure of axonal integrity. Another commonly used measure that summarizes the total diffusivity is the Trace (sum of both the RD and AX).

To the best of our knowledge, no DTI study has investigated the WM projections between mOFC and rACC, even though, as described above, mOFC and rACC are located close to each other, and are strongly connected functionally. One reason for this may be the limitation of streamline tractography. Streamline tractography does not provide information regarding the certainty of the estimated fiber tracts. Accordingly, uncertainty of generated tracks caused by increased imaging noise (i.e., diffusion signal within the gray matter (GM)) 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 GM regions. Stochastic tractography (Björnemo et al., 2002) is a Bayesian approach that addresses weaknesses of streamline tractography. This method uses a 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 areas of low uncertainty (i.e., low FA). It thus can track through fiber crossings and continue into gray matter. This

makes stochastic tractography a superior method for directly assessing connectivity between GM regions, to model and measure the anatomy of specific functional networks in the brain (Kubicki et al., 2011), as we have done here for mOFC and rACC. In addition, we examined the association between FA in mOFC-rACC connections and negative symptoms in schizophrenia. For the latter, we predicted FA alterations would be associated with severity of negative symptoms associated with defective emotional processing and social behavior in schizophrenia, particularly those involving emotion and social interactions, previously associated with mOFC and rACC (Phan et al., 2002; Jackson et al., 2006; Phan et al., 2004).

2. METHODS

Subjects

Twenty-seven patients with chronic schizophrenia were recruited from the VA Boston Healthcare System, Brockton, MA. Subjects were all male, since patients were recruited from VA population, which is mostly male. Subjects were diagnosed based on SCID-P (First et al., 2002) interviews and information from medical records, using DSM-IV criteria. Twenty-six healthy control subjects (group-matched to patients on age, sex, handedness (Edinburgh inventory (Oldfield, 1971), and parental social economic-status (PSES)) were recruited through advertisements in local newspapers, and interviewed using the SCID-NP (First et al., 2002). Demographics are shown in Table 1. All subjects met the following criteria: no history of electroconvulsive shock treatment, no history of neurological illness, no alcohol or drug dependence in the last 5 years and no abuse in the past year, no medication with deleterious effects on neurological or cognitive functions, and an ability and desire to cooperate indicated by written informed consent signed prior to study participation. Healthy control subjects were additionally screened to exclude first-degree relatives with an Axis I disorder. To evaluate negative symptoms, the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1981) was administered. The contents of SANS items for "Avolition-apathy" and "Anhedonia-asociality" are shown in the Supplemental Methods (see online supplemental materials). We used the sum of the individual ratings for analyses. Besides SANS, WRAT-III, was used in all subjects. WRAT-III is a reading subtest that measures recognition and pronunciation of printed words, and is considered to be a good estimate of premorbid IQ (Gladsjo et al., 1999). Evaluation with SANS and WRAT-III was performed at protocol entrance, with MRI scans occurring no more than one week later.

The study was approved by the local IRB committee at the VA and Brigham and Women's Hospital.

MRI Protocol and Image Processing

Detailed information for MRI protocols is included as Supplemental Material. As the first step for image processing, bilateral r-ACC and bilateral mOFC were extracted using FreeSurfer (http://surfer.nmr.mgh.harvard.edu). After ROI extraction, anatomical scans, along with corresponding ROIs were nonlinearly co-registered to DTI space, using FNIRT (http://www.fmrib.ox.ac.uk/fsl/fnirt). The details of common image processing steps are described in detail elsewhere (Kubicki et al, 2011). Then, mOFC was divided into anterior mOFC (ant mOFC), and posterior OFC (post mOFC) according to the cytoarchitecture,

connectivity, and function (Choi et al., 2004) using FreeSurfer software. The anterior border of post mOFC was determined by the most anterior coronal slice that contained rACC.

Stochastic Tractography—Once ROIs were transferred to DTI space, stochastic tractography (http://www.slicer.org)) was performed to generate WM connections. Tracts were seeded first in rACC, and filtered through mOFC, then seeded in mOFC and filtered through rACC, and both connections were used for subsequent analyses. The same procedure was performed for rACC-ant mOFC connections and for rACC-post mOFC connections. Five-hundred seeds/voxels were used for stochastic tractography. No stopping criterion for tractography was used. We obtained a probability map, based on the number of tracts per voxel, divided by the total number of tracts generated. This probability map was thresholded at 10%, to eliminate unlikely paths (Kubicki et al., 2011; Powell et al., 2006). Mean FA, RD, AX, and Trace were calculated within each tract mask to examine WM connecting mOFC and rACC. The ROIs and stochastic "cloud" are displayed in Figure 1.

Data Analysis

Relative volumes of ROI (in order to control for individual head size, absolute volumes were corrected for whole brain volumes using intracranial content (ICC) [i.e. relative volume = (absolute volume/ICC) × 100] (Kasai et al, 2003)), and measures of anatomical connectivity between regions were subjected to quantitative analysis using the Statistical Package for Social Sciences (SPSS v.19.0). First, relative volumes were analyzed with omnibus analysis of variance (ANOVA) using two within-factors of region (ant mOFC, post mOFC and rACC) and side (left and right), and one between-factor of group (schizophrenia and controls). Interactions were followed with separate repeated measures ANOVAs for each ROI with side as a within factor and group as a between factor. Finally, each ROI was compared between groups using post-hoc, one-way ANOVA. Significance was set at $p<0.00833$ after Bonferroni correction. DTI data were analyzed similarly: mean FA, RD, AX, and Trace in the four connections was analyzed using 4 separate omnibus ANOVAs with two within-factors of connection (anterior mOFC-rACC, posterior mOFC-rACC) and side, and one between-factor of group. Interactions were followed with a separate ANOVA for the connection between anterior mOFC-rACC and posterior mOFC-rACC with side as within-factor and group as between-factor. Finally, each connection was compared between groups using one-way ANOVAs, with Bonferroni's corrected significance set at $p<0.0125$. Finally, correlations between the relative volumes of ROIs and mean FA, RD, AX, and Trace values of their corresponding tracts were assessed with Pearson's correlation to examine the effect of volume on the WM variables.

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 mean FA values for specific connections that show abnormalities in group comparison, with SANS scores for the schizophrenia group using Pearson's correlation. Furthermore, we examined the association between relative volumes of ROIs and SANS scores to confirm the effect of volume change on the scores of SANS. We used $p<0.05$ as

the cutoff for reporting statistical significance, since we considered these analyses to be hypothesis driven.

Medication

Daily chlorpromazine equivalent antipsychotic dosage (Woods, 2003) was 356.5±291.7 mg, and medication was as follows: typical antipsychotic, 7.4%, atypical antipsychotic, 70.4%, both, 11.1%, unmedicated, 11.1%. The antipsychotic dosage did not correlate with mean value of FA, RD, AX, or Trace for any of the examined connections.

3. RESULTS

No significant group difference was found for the age (t_{50}=0.71, p=0.48), handedness (t_{51}=1.28, p=0.21), PSES (t_{49}=0.93, p=0.36), and WRAT-III reading subtest (t_{38}=1.64, p=0.11). Schizophrenia group showed worse score in subject's own socioeconomic status ($t_{44.1}$=5.69, p<0.001), and shorter length of education (t_{51}=3.47, p=0.001), when compared to control group.

The mean and the standard deviation (SD) for the relative volumes of the ROIs for each of the schizophrenia and healthy control group were as follows: schizophrenia group mean (SD): left ant-mOFC 0.079 (0.032), right ant-mOFC 0.111 (0.043), left post-mOFC 0.211 (0.036), right post-mOFC 0.202 (0.032), left rACC 0.150 (0.031), right rACC 0.111 (0.028); healthy control group: left ant-mOFC 0.083 (0.030), right ant-mOFC 0.116 (0.039), left post-mOFC 0.233 (0.034), right post-mOFC 0.224 (0.027), left rACC 0.149 (0.033), right rACC 0.130 (0.023). Repeated measures ANOVAs revealed a significant group effect in mOFC and rACC relative volumes (F[1,51]=13.278, p=0.001), a main effect of ROIs (F[1.447,51]=284.703, p<0.001) and a side effect (F[1,51]=7.823, p=0.007), and significant interactions between ROI and side (F[1.779,51]=34.727, p<0.0001). Post-hoc analysis revealed no significant group difference for any individual ROI volume suggesting there was no significant volume reduction in ROI gray matter volumes in schizophrenia group comparing with healthy control group.

Figure 2 shows the scatter plots for FA across the four connections for two groups. Repeated measures ANOVAs revealed significant between-group differences in FA (F[1,51]=62.969, p<0.0001), and significant interactions between group and connection (F[1,51]=9.992, p=0.003), and between side and group (F[1,51]=6.030, p=0.018), as well as connection×side×group interaction (F[1,51]=4.427, p=0.040). Post hoc analysis revealed significant differences in left anterior mOFC-rACC connections (F[1,51]=24.798, p<0.0001) and bilateral post mOFC - rACC connections (left: F[1,51]=73.431, p<0.0001; right: F[1,51]=32.261, p<0.0001). However, the connection between right ant mOFC-rACC (F[1,51]=3.047, p=0.087) did not reach statistical significance (Table 2). Comparisons between groups for the RD, AX, and Trace are shown in Table 2. The schizophrenic group showed significant FA reduction in left ant mOFC-rACC connection and bilateral post mOFC-r ACC connections; RD increase in left anterior mOFC-rACC connections and bilateral post mOFC-rACC connections; and Trace increase in left post mOFC-rACC connections. No significant mean AX change was observed.

No significant association was observed between ROIs' relative volume and mean FA, RD, AX, and Trace in the tracts that connect these ROIs.

In schizophrenia, mean FA reductions in left post mOFC-rACC connections were associated with the sum of item scores for avolition-apathy (R=–0.426, p=0.027, n=27) and for anhedonia-asociality (R=–0.396, p=0.041, n=27), from the SANS (Figure 3). On the other hand, no association was found between ROIs' relative volume and scores on the SANS.

4. DISCUSSION

Using stochastic tractography, we examined WM mOFC-rACC connections in patients diagnosed with chronic schizophrenia. Results indicate FA and RD abnormalities in left anterior mOFC-rACC connections and bilateral posterior mOFC-rACC connections; and Trace abnormalities in left posterior mOFC-rACC connections in patients with schizophrenia. Although ROI volumes showed significant reduction in schizophrenia, no association was found between ROI volumes and WM measures for any of the tracts, further indicating that GM and WM pathologies might not be related. Furthermore, FA reduction in left posterior mOFC-rACC connections was associated with more severe avolition-apathy and anhedonia-asociality. Accordingly, the observed FA reductions in left posterior mOFC-rACC connections were associated with more severe negative symptoms related with defective emotional processing and social behavior.

Previous studies have shown that FA reductions in corpus callosum (Hubl et al., 2004; Rotarska-Jagiela et al., 2008), cingum bundle (Hubl et al., 2004), arcuate fasciculus (Hubl et al., 2004), superior longitudinal fasciculus (Seok et al., 2007), and inferior fronto-occipital fasciculus (Szeszko et al., 2008) are correlated with more severe psychotic symptoms in schizophrenia. The present results are consistent with these studies in suggesting the association between FA reduction and symptom severity in schizophrenia. FA reduction has been associated with axon death, myelin damage, damage to the axon membrane, and reduced "fiber coherence" (Kubicki et al., 2007). In addition to FA, we used more specific measures of axonal and myelin integrity, AX and RD respectively. Patients with schizophrenia showed abnormally increased RD without change in AX compared to controls in left anterior mOFC-rACC and bilateral posterior mOFC-rACC connections. This might suggest that abnormalities in the fibers of these connections are more likely underpinned by myelin abnormalities as opposed to damage to the axon membrane (Song et al., 2002). Furthermore, as Trace is the sum of both the RD and AX and reflects total diffusivity, the observed Trace increase in patients with schizophrenia appears to be driven by RD increase. If the observed diffusion abnormalities in the mOFC - rACC connection were indeed the result of myelin damage, this might result in slowed impulse conduction (Roy et al., 2007) and would, accordingly, likely affect various brain functions through the mechanism of conduction delays (Whitford et al., 2011).

FA reduction in WM between left post mOFC and left rACC was associated with severity of negative symptoms including avolition-apathy and anhedonia-asociality. MOFC and ACC are thought to be involved in the decision-making circuit (Rushworth et al., 2011), and severity of avolition-apathy has previously been reported to be significantly associated with

decisional capacity in schizophrenia (Moser et al., 2002). Therefore, abnormal connectivity between left posterior mOFC and left rACC might affect necessary interactions within the decision-making neural circuit and, as a result, produce symptoms of avolition-apathy. Additionally, functional connectivity between OFC and ACC likely plays a role in emotional processing (de Marco et al., 2006), and thus abnormal anatomical connectivity between OFC and ACC might result in deficits in emotional processing. For example, social anhedonia is associated with emotional processing in schizophrenia (Germine et al., 2011). Hence, we speculate that the observed abnormalities in connections between mOFC and rACC may be manifested by concomitant deficits in emotional processing in schizophrenia.

Abnormalities observed in left anterior mOFC-ACC and bilateral posterior mOFC-rACC connections, and the association between degree of posterior mOFC-ACC dysconnectivity and symptom severity, supports our hypothesis that WM connections between mOFC and rACC may be abnormal, and that these abnormalities may be associated with defective emotional processing and social behavior in schizophrenia. Further studies examining associations between WM fiber connectivity and functional connectivity between OFC and ACC, along with their clinical correlates in schizophrenia, may further reveal the role of this pathway in the pathology of schizophrenia.

Limitations

The following limitations should be considered when interpreting our results. First, our population is limited to male participants. Second, most patients were medicated. However, we found no correlation between medication and DTI indices. Finally, we performed correlation analyses between the connections that showed reduced FA compared with HC group and the 5 SANS subscales. However, the results of the correlation analyses were not corrected for multiple comparisons, thus, we consider them exploratory. We believe that our non-corrected results provide clues regarding relationship between negative symptoms and abnormal connectivity between mOFC and rACC, however future studies will have to replicate these findings.

5. CONCLUSION

In summary, we reported FA reductions, and RD and Trace increases in several connections between mOFC and rACC, suggesting that dysmyelination may contribute to abnormal connectivity in patients diagnosed with chronic schizophrenia, compared with matched healthy controls. In addition, association between FA reduction and severity of avolition-apathy and anhedonia-asociality, further suggests an association between posterior mOFC-rACC dysconnectivity and defective emotional processing and social behavior in schizophrenia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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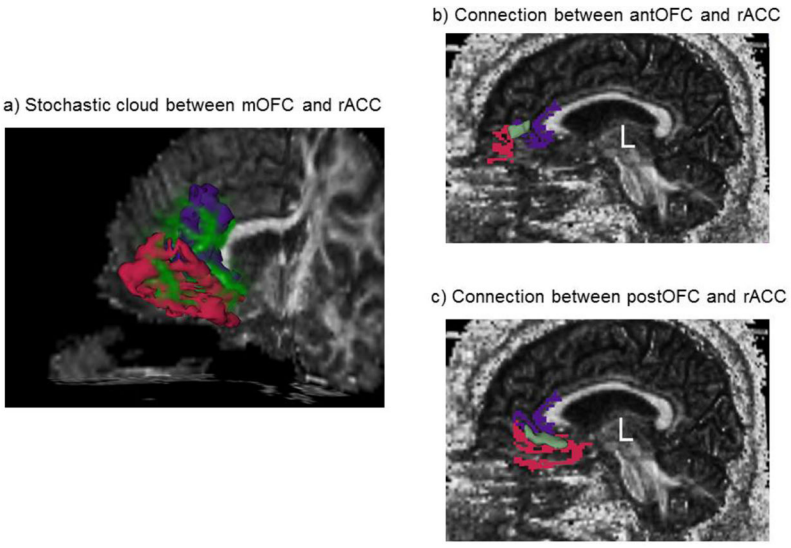

Figure 1.

The stochastic cloud connecting medial orbitofrontal cortex (mOFC) and rostral anterior cingulate cortex (rACC). The red structure is mOFC, the purple is rACC, and the light green is the stochastic cloud connecting the mOFC and the rACC.

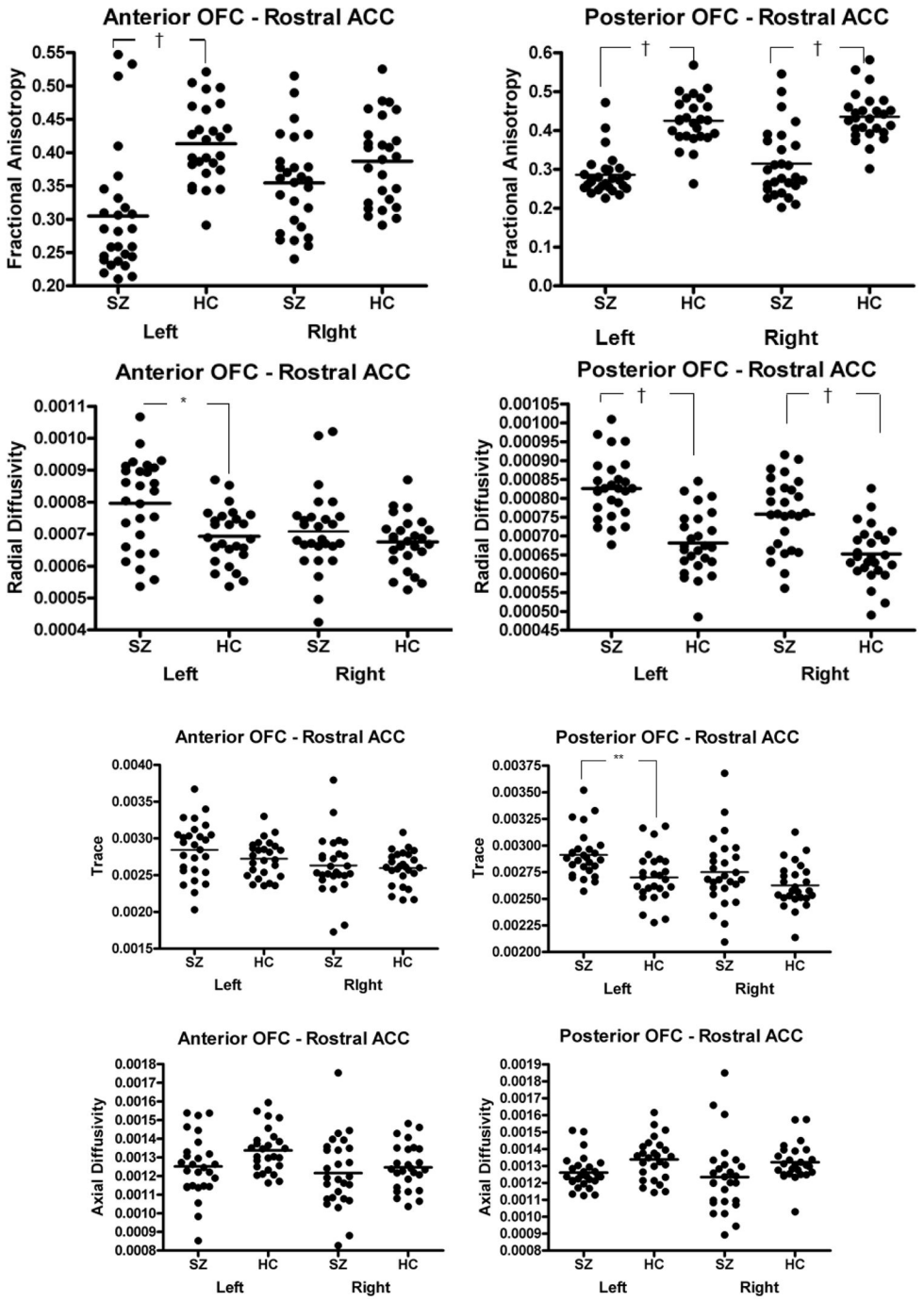

Figure 2.

Scatter plots of mean FA, Trace, Axial Diffusivity, and Radial Diffusivity for schizophrenia and for the healthy control group. Abbreviations: FA = fractional anisotropy; OFC = orbitofrontal cortex; ACC = anterior cingulate cortex; SZ = schizophrenia group; HC = healthy control group. *p = 0.002, **p = 0.001, †p < 0.001.

Note that Figure 2 is continued on a second image.

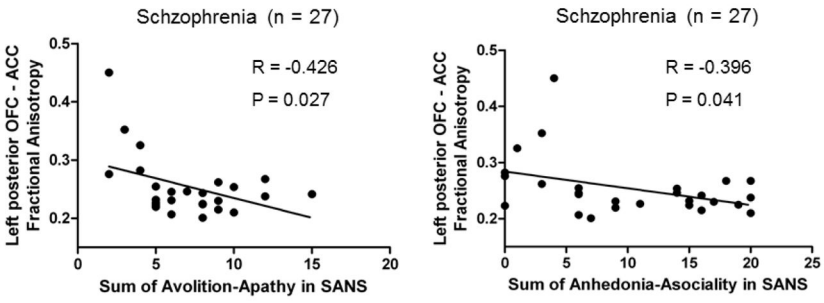

Figure 3.

Correlations between mean fractional anisotropy (FA) and clinical symptoms. In the schizophrenia group, reduced FA between left posterior medial orbitofrontal cortex (mOFC) and left rostral anterior cingulate cortex (rACC) are associated with more severe avolition-apathy and anhedonia-asociality symptoms.

Table 1

Demographic and clinical characteristics of study groups

Variable	Mean (SD)		Independent t test		
	SZ group (n = 27)	HC group (n = 26)	d.f.	*t*	*P*
Age (year)	40.65 (10.18)	38.62 (10.61)	50	0.707	0.483
Handedness [a)]	0.72(0.24)	0.80(0.17)	51	1.276	0.208
Socioeconomic status [b)]					
Subject's own	3.37 (1.08)	1.96 (0.68)	44.107	5.691	<0.001
Parental	2.59 (1.12)	2.29 (1.20)	49	0.928	0.358
Education (school year)	13.28 (1.81)	15.04 (1.89)	51	3.468	0.001
WRAT-III reading [c)]	98.08 (12.29)	104.33 (10.55)	38	1.639	0.109
Age at symptom onset (years old)	24.42 (5.74)[d)]	NA			
Duration of illness (years)	16.57 (10.34)[e)]	NA			
Antipsychotic medication dosage [f)]	393.28 (309.82)	NA			

Abbreviation: SZ, 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 = 26.

[e)] n = 23.

[f)] Chlorpromazine equivalent (mg).

Table 2

Mean fractional anisotropy, mode, trace, axial diffusivity and radial diffusivity in the SZ and HC groups

		SZ group (n = 27)		HC group (n = 26)		1-factor ANOVA	
Connection	**Hemisphere**	**Mean**	**SD**	**Mean**	**SD**	$F_{1,51}$	*P*
Mean Fractional Anisotropy [a)]							
Anterior mOFC – rACC	Left	0.305	0.095	0.413	0.059	24.798	< 0.001* [e)]
	Right	0.354	0.071	0.387	0.065	3.047	0.087
Posterior mOFC – rACC	Left	0.286	0.055	0.425	0.063	73.431	< 0.001* [e)]
	Right	0.314	0.090	0.435	0.061	32.261	< 0.001* [e)]
Mean radial diffusivity [b)]							
Anterior mOFC – rACC	Left	0.000797	0.000140	0.000693	0.000088	10.222	0.002* [e)]
	Right	0.000708	0.000127	0.000676	0.000082	1.241	0.271
Posterior mOFC – rACC	Left	0.000826	0.000082	0.000681	0.000084	40.368	<0.001* [e)]
	Right	0.000758	0.000095	0.000652	0.000075	20.193	<0.001* [e)]
Mean axial diffusivity [c)]							
Anterior mOFC – rACC	Left	0.00125	0.00016	0.00134	0.00012	4.809	0.033
	Right	0.00122	0.00019	0.00125	0.00012	0.469	0.497
Posterior mOFC – rACC	Left	0.00126	0.000098	0.00134	0.00012	6.517	0.014
	Right	0.00123	0.00021	0.00132	0.00011	3.576	0.064
Mean Trace [d)]							
Anterior mOFC – rACC	Left	0.00284	0.00038	0.00272	0.00025	1.863	0.178
	Right	0.00263	0.00041	0.00260	0.00023	0.149	0.701
Posterior mOFC – rACC	Left	0.00291	0.00022	0.00270	0.00023	11.502	0.001* [e)]
	Right	0.00275	0.00032	0.00262	0.00021	2.733	0.104

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

[a)]Repeated-measures ANOVA of mean FA, mode and trace with group (SZ 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 revealed a main effect for group ($F [1, 51] = 62.969$; $P < 0.0001$). There were significant two way interactions for group × connection ($F [1, 51] = 9.992$, $P = 0.003$) and side × group ($F [1, 51] = 6.030$, $P = 0.018$), and three way interaction for side × connection × group ($F [1, 51] = 4.427$, $P = 0.040$).

[b] Repeated measures ANOVAs revealed significant between-group differences in radial diffusivity ($F [1, 51] = 28.839$, $p < 0.0001$), and significant main effect of side ($F [1, 51] = 12.142$, $p = 0.001$), and interactions between group and connection ($F [1, 51] = 7.636$, $p = 0.008$).

[c] Repeated measures ANOVAs revealed significant between-group differences in axial diffusivity ($F [1, 51] = 8.619$, $p = 0.005$), although there was no significant main effect or interaction.

[d] Repeated measures ANOVAs revealed significant between-group differences in Trace ($F [1, 51] = 6.025$, $p = 0.018$), and significant main effect of side ($F [1, 51] = 9.484$, $p = 0.003$).

[e] *Statistically significance after corrected by Boferroni's correction.