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Alteration of Gray Matter Microstructure in Schizophrenia

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Abstract

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Compliance with ethical standards

Disclosure of potential conflicts of interest

The Authors Seitz Johanna, Rath Yogesh, Lyall Amanda, Pasternak Ofer, del Re Elisabetta C, Niznikiewicz Margaret, Nestor Paul, Seidman Larry J, Petryshen Tracey L, Mesholam-Gately Raquelle I, Wojcik Joanne, McCarley Robert W, Shenton Martha E, Koerte Inga K, and Kubicki Marek have declared that there are no conflicts of interest in relation to the subject of this study.

Research involving human participants and/or animals

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed Consent

Informed consent was obtained from all individual participants included in the study.

Purpose—Neuroimaging studies demonstrate gray matter (GM) macrostructural abnormalities in patients with schizophrenia (SCZ). While ex-vivo and genetic studies suggest cellular pathology associated with abnormal neurodevelopmental processes in SCZ, few in-vivo measures have been proposed to target microstructural GM organization. Here, we use diffusion heterogeneity- to study GM microstructure in SCZ.

Methods—Structural and diffusion magnetic resonance imaging (MRI) were acquired on a 3 Tesla scanner in 46 patients with SCZ and 37 matched healthy controls (HC). After correction for free water, diffusion heterogeneity as well as commonly used diffusion measures FA and MD and volume were calculated for the four cortical lobes on each hemisphere, and compared between groups.

Results—Patients with early course SCZ exhibited higher diffusion heterogeneity in the GM of the frontal lobes compared to controls. Diffusion heterogeneity of the frontal lobe showed excellent discrimination between patients and HC, while none of the commonly used diffusion measures such as FA or MD did.

Conclusions—Higher diffusion heterogeneity in the frontal lobes in early SCZ may be due to abnormal brain maturation (migration, pruning) before and during adolescence and early adulthood. Further studies are needed to investigate the role of heterogeneity as potential biomarker for SCZ risk.

Keywords

diffusion MRI; heterogeneity; schizophrenia; neurodevelopment; gray matter

Introduction

Schizophrenia (SCZ) is a severe psychiatric disorder with significant consequences for affected patients and society as a whole (Ratnasingham et al., 2013; Rössler, Salize, van Os, & Riecher-Rössler, 2005; Whiteford et al., 2013). Patients with SCZ exhibit several macrostructural brain abnormalities including reduced regional gray matter volume and enlarged ventricles. The biological interpretations of these macrostructural gray matter alterations include abnormal cortical development, differential maturational trajectories (e.g., Nesvag et al., 2014; Vogeley et al., 2000), and possible neurodegeneration and/or accelerated aging (Assunção Leme et al., 2013; Egashira et al., 2014; Hulshoff Pol & Kahn, 2008). However, since volumetric measures are biologically non-specific and appear to be present at all stages of the illness, associations of macrostructural changes with potential microstructural pathology have been difficult.

Diffusion tensor imaging (DTI) (Basser, Matielo, & Bihan 1996; Pierpaoli & Basser, 1996) has been demonstrated to be sensitive to microstructural alterations (Spoleitini et al., 2011). DTI provides information about the motion of water within brain tissue by quantifying the extent and directional preference of diffusion. Brain alterations at the cellular level lead to local modifications in water diffusion and can be detected by DTI even when macrostructural features do not change (Fjell et al., 2008). So far, DTI has primarily been used to evaluate white matter microstructure in SCZ (Kubicki et al., 2007) and very few SCZ

gray matter DTI studies have been conducted (Anderson et al., 2013; Lee et al., 2009; Moriya et al., 2010; Park, Park, Kim, & Kim, 2014; Shin et al., 2006).

The most common DTI metrics that are being used to evaluate microstructural brain alterations include fractional anisotropy (FA), an index of white matter axonal organization and coherence, and mean diffusivity (MD), an index of overall white matter water content. While diffusion anisotropy and orientation of the fibers are of interest in white matter, both these measures are less relevant in gray matter. This is because the diffusion properties of gray matter reflect the diffusion of water hindered by cell bodies and their processes, while in white matter diffusion properties reflect the diffusion of water within bundles of long myelinated axons. Therefore, in gray matter there is no preferred direction of orientation that can be measured with current clinical imaging data resolution. It has been shown that the diffusion measures within the same anatomical structure in gray matter vary from voxel to voxel much more than in white matter (Vollmar et al., 2010). This variance in diffusion properties does not only indicate that FA or MD of a single voxel may not be appropriate to study gray matter, but it also makes these metrics insensitive to the detection of subtle abnormalities in the cortex, even when averaged over larger regions.

Therefore, we suggest that in addition to existing diffusion indices, it is important to consider DTI measurements that would capture cortical organization on a bigger scale, i.e. inter, rather than intra-voxel. For example, Kalus et al. (Kalus et al., 2004; Kalus, Slotboom, Gallinat, Federspiel, et al., 2005; Kalus, Slotboom, Gallinat, Wiest, et al., 2005) conducted inter-voxel coherence studies and they report reduced coherence in the amygdala and parahippocampal regions in patients with SCZ, which they interpreted to represent differences in local contents of ordered fiber systems.

Another possible measurement capturing inter-voxel organization was recently introduced by Rath et al. (2014). It is derived from the diffusion signal and called “heterogeneity”. Heterogeneity is a statistical measure that determines the variability of microstructural gray matter tissue properties reflected by diffusion measures within a given region of interest (ROI); e.g. the heterogeneity of FA (HFA) reflects the variability of FA within a defined ROI. It can therefore separate the effect of anisotropic diffusion from that of overall measure of diffusivity (MD). In contrast to other inter-voxel coherence measurements, one does not need to choose reference voxels and it can therefore be computed in arbitrarily large or small regions (e.g. for the four cortical lobes).

Normal, healthy cortex is characterized by relatively low heterogeneity of diffusion properties in gray matter, suggesting a consistent uniform tissue organization (Rath et al., 2014). However, less consistent cellular organization within gray matter tissue, a result of possible age-dependent reorganization or faulty neurodevelopment of the cortex, would lead to more heterogeneous diffusion behavior that would be reflected as greater variability of diffusion properties, resulting in increased heterogeneity. Thus, heterogeneity has the potential to serve as a more sensitive indicator of microstructural organization of gray matter tissue than FA or MD to detect alterations in tissue organization, even in the absence of macrostructural volumetric changes.

The aim of the current study is to use heterogeneity to investigate gray matter microstructural organization in patients with SCZ. For reasons mentioned above, we expect our method to be more sensitive for differentiating between groups than traditional diffusion measurements, such as FA, MD or macrostructural gray matter measurements, i.e., cortical volume (Arnold, 2001). We will apply heterogeneity in a cross-sectional study design to patients at different disease stages (early course and chronic) and well matched healthy control (HC) group. We predict higher gray matter heterogeneity in patients with SCZ (but not necessarily higher FA or MD), which we propose would reflect abnormal cortical organization in SCZ (Teffer & Semendeferi, 2012).

Methods

Participants

Forty-six patients (9 females, 37 males) with SCZ and thirty-seven healthy control subjects (HC) (10 females, 27 males) were recruited from the Boston area. The entire sample was separated into two sub groups—patients within three years of onset of SCZ (19 patients, 15 HC) and patients with chronic SCZ (27 patients, 22 HC) (Supplement 1). Patients with early course SCZ were recruited via the Boston Center for Intervention Development and Applied Research (CIDAR study) from outpatient clinics. Patients with a more chronic illness were recruited from the Veteran Affairs Boston Healthcare System, Brockton Division, MA.

Groups were matched on age, sex, handedness, parental socioeconomic status, and estimated premorbid intelligence (Reading scale of Wide Range Achievement Test- 3 (Wilkinson, 1993)) (Table 1). Diagnoses were based on a diagnostic interview using the Structured Clinical Interview for the DSM-IV-TR, Research Version (SCID) (First, Spitzer, Gibbon, & Williams, 2002b) for ages >18, or the KID-SCID (Hien et al., 1994) (for subjects 15–17 years of age). Patients were excluded if they had a history of electroconvulsive therapy within the past 5 years. 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, Spitzer, Gibbon, & Williams, 2002a) 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 as the circumstances required medications such as sleeping medications or anxiolytic agents, or 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.

For all subjects, exclusion criteria included sensory-motor handicaps (e.g. severe visual or auditory problems), 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.

The Institutional Review Boards of the Veteran Affairs Boston Healthcare System, Brigham and Women's Hospital, Beth Israel Deaconess Medical Center, Massachusetts Department of Mental Health Central Office Research Review Committee, and Harvard Medical School approved the study. Each subject or legal guardian for those under 18 years provided understanding and written informed consent before participating.

Image Acquisition

All images were acquired on a 3 Tesla whole body General Electric MRI scanner (GE Medical Systems, Milwaukee). The MRI sequences included a high-resolution 3D T1 (IR-FSPGR, TR 7.8 ms, TE 3 ms, TI 600 ms, flip angle 10°, FOV matrix size 256x256, 176 slices, 1mm slice thickness). Diffusion weighted images (DWIs) were acquired using a twice refocused echo-planar imaging sequence (TR 17 s, TE 80 ms, flip angle 90°, FOV matrix size 144x144, 85 slices, 1.7 mm slice thickness, 51 gradient directions with $b=900$ s/mm² and eight baseline scans with $b=0$ stacked at the beginning of the image sequence). During the course of the study a scanner software upgrade took place. Even so HC and patients with SCZ did not differ in how many subjects were scanned before and after scanner upgrade (see Table 1), we included scanner update as a covariate in our analysis.

Image Processing

For further information on the imaging process, see Figure 1. The data was visually inspected for artifacts and signal drops. We checked our data for outliers (3 x interquartile range) and found that no subjects needed to be excluded from the analyses.

The T1 images were manually realigned and parcellated into 176 gray matter, white matter, and cerebrospinal fluid regions using the FreeSurfer software (<http://surfer.nmr.mgh.harvard.edu/>). The DWIs were corrected for motion by means of affine registration with a reference b0 volume (FLIRT, FSL, Oxford; <http://fsl.fmrib.ox.ac.uk/fsl> (Jenkinson, Bannister, Brady, & Smith, 2002)). Diffusion gradients were compensated for rotation and distortion. Next, the T1 FreeSurfer segmentations were registered to the DWIs using non-linear registration (FNIRT, FSL, Oxford; <http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FNIRT>).

To minimize the impact of partial volume effects on diffusion measures, we applied a free water correction to the DWI data (Pasternak, Sochen, Gur, Intrator, & Assaf, 2009). The removal of the free water influence is especially important for gray matter studies, because it allows for more accurate diffusion parameters that are less influenced by the partial volume effects of extracellular components, and are thus more specific to cellular gray matter structure (Koo et al., 2009). For the free water correction, the diffusion signal is separated into two compartments - the free water and the tissue compartment. It is assumed that the diffusion of water molecules in the free water compartment is not restricted by any

surroundings and can therefore be described as Gaussian distributed Brownian motion (Beaulieu, 2002) with a self-diffusion coefficient of approximately $3 \times 10^{-3} \text{ mm}^2/\text{s}$ (Holz, Heil, & Sacco, 2000; Mills, 1973). The diffusion in this environment is much greater than in cortical tissue where cellular processes lead to a hindered displacement profile (Assaf & Basser, 2005; Helenius et al., 2002). This free water contribution can be removed from the overall diffusion signal, which is then described by the classical diffusion tensor model (Basser & Pierpaoli, 1996). The diffusion parameters, such as FA and MD, are then calculated for this remaining tissue compartment for each voxel. These free water corrected diffusion measures will most likely capture tissue processes or extracellular processes in proximity to cellular membranes and therefore also specific to tissue changes (Pasternak et al., 2014).

Afterward free water correction, heterogeneity was calculated. Heterogeneity is mathematically defined as:

$$H(m) = \frac{1}{N^2} \sum_{i=1}^N \sum_{j=1}^N \|m_i - m_j\|$$

where N is the number of voxels in the ROI, and m is the value of a given diffusion measurement (such as FA) in a voxel, indexed by i or j . Heterogeneity describes the statistical variability of a diffusion measurement in an ROI, while being more robust than classical variability measures like variance (Rathi et al., 2014).

The heterogeneity of FA (HFA) for four cortical lobes (frontal, parietal, temporal, occipital) was calculated using Matlab (TheMathWorks). The four cortical lobes were delineated by combining all corresponding FreeSurfer ROIs (e.g. the frontal lobe was generated by combining the 12 right frontal gray matter FreeSurfer ROIs with the 12 left frontal gray matter FreeSurfer ROIs) (Desikan et al., 2006).

Statistical Analysis

Statistical Analyses were performed with GraphPad Prism 6 (GraphPadSoftware, 2014) and the Statistical Package for Social Sciences version 22.0 (IBM Corp, 2013).

To replicate and extend the findings of Rathi et al. (2014), we focused our initial analysis on the association of HFA, FA, MD, and volume with age by calculating correlations (Pearson r) for the entire SCZ and HC group separately, then testing with an F-Test if the correlation coefficients were significantly different from zero (adjusted $p < .0063$).

Next, we separated the entire sample into the two sub-groups (patients within three years of onset versus patients with chronic SCZ and their matched HCs).

We analyzed group differences using MANCOVAs (one for each measurement-HFA, FA, MD, volume) for both sub-groups. The independent variable of interest was group affiliation (SCZ versus HC), whereas the dependent variables were HFA/FA/MD/volume of the frontal, parietal, temporal, and occipital regions, while age, gender and scanner update were included as covariates. In the case of a significant group difference, we examined this further

using post hoc ANCOVAs for the four cortical lobes with group as independent variable, HFA as dependent variable, and age, scanner update, and gender as covariates.

In the case of a significant ANCOVA, receiver operating characteristics (ROC) curves were created for HFA, FA, MD, and volume and then the areas under the ROC curve (AUCs) were calculated. ROC curves provide a way to quantify how well a measure, for instance heterogeneity, can discriminate between two groups, in our case the HC and patient groups. AUCs were interpreted following Hosmer and Lemeshow (Hosmer & Lemeshow, 2000), where higher values stand for better prediction.

To further elucidate the association of group differences with clinical variables, we used partial correlation analysis (corrected for age) in case of significant group differences between diffusion measurements and duration of illness, medication dose, and age of onset for patients with early course SCZ.

Results

Correlation of HFA with age

There was a positive association between both HFA and FA with age, whereas MD and volume exhibited negative correlations with age in patients and HC (Table 2).

Difference between SCZ and HC

Patients with chronic SCZ—None of the MANCOVAs showed a significant group difference ($p < .013$, Bonferroni corrected for four tests) for HFA, FA, MD, and volume between patients with chronic SCZ and controls (Table 3).

Patients with early course SCZ—The MANCOVA for HFA showed significant group differences ($p < .013$, Bonferroni corrected for four tests) ($F = 5.50$, $df_1 = 4$, $df_2 = 26$, $p = .0020$), whereas the MANCOVAs for FA, MD, and volume did not (Table 3).

Due to the significant group effect, we conducted post hoc ANCOVAs for the frontal, parietal, temporal, and occipital regions with group as the independent variable, HFA as the dependent variable, and age, scanner update, and gender as covariates. Only the HFA of the frontal region showed significant ($p < .013$, Bonferroni corrected for four tests) group differences ($F = 10.68$, $df = 1$, $p = .0030$) while the HFA of the occipital ($F = 6.44$, $df = 1$, $p = .017$), parietal ($F = .15$, $df = 1$, $p = .70$) and temporal ($F = 6.44$, $df = 1$, $p = .28$) regions were not significant. For descriptive statistics please see Table 4.

Furthermore, HFA of the frontal region demonstrated excellent discrimination ($AUC = 0.82$, $p = .023$) between patients with SCZ and HC (Figure 2). Whereas AUC analyses of FA frontal ($AUC = 0.73$, $p = .43$), MD frontal ($AUC = .58$, $p = .43$) and volume frontal ($AUC = .55$, $p = .64$) showed poorer discrimination.

Additional analyses—The correlation analysis between HFA and age of onset ($r(10) = .24$, $p < .45$), duration of illness ($r(10) = .38$, $p < .22$), and medication dose ($r(10) = .24$, $p < .45$) did not show any significant results.

Discussion

The results of the present study show that patients with early course SCZ exhibit significantly greater HFA in the frontal lobe compared to HC and that HFA is very sensitive in group discrimination. We did not find any group differences for any other parameter, nor for the patients with chronic SCZ. Heterogeneity is a way of statistically determining the distribution of diffusion properties. Please keep in mind that the term “heterogeneity” has widely been used to describe genetic or clinical “heterogeneity” in patients with chronic schizophrenia (Dacquino, De Rossi, & Spalletta, 2015; Jouan et al., 2013; Liang & Greenwood, 2015). However, we refer to our statistical method of data evaluation which we believe can provide insights into the microstructure of gray matter.

Higher heterogeneity in frontal areas in early course SCZ patients could be indicative of aberrant maturational processes that preceded the transition to psychosis. A number of post mortem studies have reported that patients with SCZ have fewer inhibitory synapses and display excessive pruning of excitatory synapses in prefrontal areas, resulting in increased neuronal density and fewer dendrites and synapses (N. C. Andreasen, 2010; Rapoport, Giedd, & Gogtay, 2012; R. C. Roberts, Barksdale, Roche, & Lahti, 2015). These changes, in turn, could result in cortical microstructural disorganization in patients with SCZ, occurring during brain maturation which might be reflected as increased heterogeneity in the gray matter.

The findings of early microstructural alterations in SCZ are in line with the neurodevelopmental theory, which postulates that genetic susceptibility and early environmental risk factors may alter the normal maturational trajectory of the brain development, which then leads to the onset of SCZ (Feinberg, 1983; Lewis & Levitt, 2002; Nonaka, Ichinose, Kinoshita, & Nakane, 2013; Rapoport, Addington, Frangou, & Psych, 2005; Rapoport et al., 2012; Sipos et al., 2004; Sullivan, Kendler, & Neale, 2003; Thermenos et al., 2013; Weinberger, 1987). It is also well established that frontal regions are the last to develop and that the elimination of synapses in frontal lobe regions continues beyond adolescence into the second decade of life (Gogtay et al., 2004; Huttenlocher & Dabholkar, 1997; Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008; Petanjek et al., 2011). Our findings are in line with these studies, showing group differences in the frontal lobe only. Heterogeneity may thus reflect these maturational changes and it may therefore be a potential biomarker for early disease stages, or maybe even increased risk for transition to psychosis.

More importantly, heterogeneity is also a useful tool because it allows excellent discrimination between patients with early course SCZ and HC, and in this regard outperforms classical measurements, such as FA, MD and volume. It is crucial to find early diagnostic biomarker of SCZ, because intervention strategies are more likely to be successful in early disease states (McEvoy, 2007), and as such, heterogeneity might be a promising in vivo biomarker for increased risk for schizophrenia.

The absence of group differences in the chronic SCZ patients may indicate a lack of progressive cellular pathology in the gray matter. The existence of progressive,

neurodegenerative cellular pathology continues to be the matter of active debate in SCZ. Although there are no classical neurodegenerative signs such as gliosis (G. Roberts & Harrison, 2000) or neurofibrillary tangles reported (Bozikas, Kovari, Bouras, & Karavatos, 2002), cortical thinning in SCZ has been suggested to be the result of accelerated aging (2001). Present MRI evidence, however, does not clearly support the neurodegenerative hypothesis. Multiple studies show progressive gray matter reductions (in widespread cortical areas), while others find either stable or minimal gray matter group differences with age (Brans et al., 2008; Hulshoff Pol & Kahn, 2008; Kubota et al., 2011; Olabi et al., 2011; van Haren et al., 2008). However, even this progressive volume loss, if present, is being argued to be more accentuated during first few years after disease onset, and then normalizing afterwards (N. C. Andreasen et al., 2011; Bose et al., 2009; Kubota et al., 2011). This view is also consistent with the clinical profile of the disease, where after the stabilization of symptoms, no observable cognitive deterioration is seen (Jeste, Wolkowitz, & Palmer, 2011; Napal et al., 2012).

Limitations and future directions

Our study has several limitations. First, we employ a cross-sectional study design, which limits our ability to draw conclusions about the developmental trajectories of SCZ pathophysiology. Second, our population does not include at-risk subjects, it is thus possible that the changes described herein might reflect acute alterations related to disease-onset, stress, or an acute reaction to antipsychotic treatment, rather than a neurodevelopmental pathology.

Additionally, using diffusion imaging in gray matter may lead to partial volume effects. As described in the method section, we have taken multiple precautions to minimize this effect. We used high resolution diffusion data and a free water correction. This correction minimizes partial volume effects, and therefore ensures that changes in gray matter heterogeneity are less influenced by edema, atrophy or neuroinflammation (Pasternak et al., 2009). However, even though free water has widely been used (Bergamino, Pasternak, Farmer, Shenton, & Hamilton, 2016; Metzler-Baddeley, O'Sullivan, Bells, Pasternak, & Jones, 2012; Pasternak et al., 2014; Pasternak, Westin, Dahlben, Bouix, & Kubicki, 2015) the model has limitations itself. The assumption that there is no exchange between compartments is a simplification not accounting for potential differences in membrane permeability (Kochunov et al., 2014). Further studies are therefore needed to combine our model with more sophisticated approaches (Kochunov et al., 2014; Zhu et al., 2014).

Additional longitudinal studies are needed to determine the role of heterogeneity as a potential biomarker for alterations relating to onset of SCZ. Furthermore, it is unclear which effect chronic administration of medication has on heterogeneity. It is therefore possible that a longer period of medication could influence the lack of findings in the chronic group (Ho, Andreasen, Ziebell, Pierson, & Magnotta, 2011). Future studies that include a group of unmedicated patients with SCZ are thus needed.

Finally, heterogeneity may be useful not only for the investigation of SCZ, but also in other diseases, such as brain tumor or Alzheimer's disease, to help detecting early changes in cellular organization. In fact, a recent study (Walker-Samuel, Orton, Boulton, & Robinson,

2011) has shown subtle changes in tissue organization in brain tumor, measured through heterogeneity of MR signal.

Conclusion

In summary, we observed higher heterogeneity, a novel measure of microstructure, in the gray matter of the frontal lobe in patients with early course SCZ, whereas commonly used measures, such as FA, MD or volume lacked sensitivity. These findings suggest that gray matter alterations in early course SCZ may be associated with abnormalities in synaptic organization or pruning. Future studies are needed to establish heterogeneity as a neuroimaging marker of SCZ risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.**Image processing**

(A) Diffusion images were motion, distortion and rotation corrected (FLIRT, FSL, Oxford; <http://fsl.fmrib.ox.ac.uk/fsl> (Jenkinson et al., 2002)) and (B) structural images were realigned and parcellated using FreeSurfer (<http://surfer.nmr.mgh.harvard.edu/>). (C) This segmentation was non-linearly registered (FNIRT, FSL, Oxford; <http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FNIRT>) to the diffusion images. A free water correction was applied to separate the signal into a “free water” signal (D) and the tissue tensor map (E). FA and MD were calculated for each voxel of this tissue tensor map. Afterwards heterogeneities of FA and MD were computed for the frontal, parietal, temporal and occipital lobes.

Fig. 2.
Area under the curve analysis
HFA of the frontal region demonstrated excellent discrimination between patients with SCZ and HC.

Table 1

Demographic characteristics for patients with schizophrenia (SCZ) and healthy control individuals (HC)

	SCZ	HC	t	df	p
Number	46	37	-	-	-
Age (years)	36.07 ± 14.01 ^a	36.27 ± 12.51 ^a	-.070	81	.95
(Age range)	(15.63–56.92)	(17.37–53.42)	-	-	-
Gender	9f, 36m	10f, 27m	.65	1	.42
Handedness	40 left, 3 both, 3 right	36 right 1 both	3.27	2	.20
Parental socioeconomic status (PSES) ^b	2.52 ± 0.19 ^a	2.25 ± 0.16 ^a	1.07	80	.29
premorbid IQ (Wilkinson, 1993)	105.80 ± 2.69 ^a	104.50 ± 2.93 ^a	0.31	61	.76
Scanner update (before/after)	25/21	17/20	.58	1	.45
Age of onset	24.26 ± 7.59 ^a	-	-	-	-
Duration of illness SCZ	9.15 ± 10.25 ^a	-	-	-	-
Medication dose SCZ (chlorpromazine equivalent dose) ^c	603.40 ± 913.90 ^a	-	-	-	-
SANS ^d	32.05 ± 16.95 ^a	-	-	-	-
SAPS ^e	27.18 ± 24.03 ^a	-	-	-	-

^aMean ± Standard deviation;

^bHigher numbers represent lower PSES;

^cFollowing the international consensus study of antipsychotic dosing (Gardner, Murphy, O'Donnell, Centorrino, & Baldessarini, 2010);

^dSANS= The Scale for the Assessment of Negative Symptoms (N. C. Andreasen, 1984a);

^eSAPS= Scale for the Assessment of Positive Symptoms (N. C. Andreasen, 1984b)

Clinical and demographic information was not available for all subjects participating in this study

Table 2

Correlation coefficients (Pearson) for patients with schizophrenia (SCZ) and healthy control individuals (HC) of HFA, FA, MD and Vol with age

	HFA SCZ	HFA HC	FA SCZ	FA HC	MD SCZ	MD HC	Vol SCZ	Vol HC
Frontal	0.63 *	0.77 *	0.54 *	0.66 *	-0.69 *	-0.58 *	-0.58 *	-0.46 *
Parietal	0.67 *	0.51 *	0.71 *	0.54 *	-0.57 *	-0.48 *	-0.41 *	-0.44 *
Temporal	0.41 *	0.34	0.48 *	0.56 *	-0.50 *	-0.40	-0.47 *	-0.47 *
Occipital	0.63 *	0.25	0.67 *	0.48 *	-0.55 *	-0.21	-0.032	-0.39

* indicates statistically significant correlation with $p < .0063$ (Bonferroni Correction, $n=8$)

HFA= heterogeneity of fractional anisotropy; FA= fractional anisotropy; MD= mean diffusivity (in $10^{-3}\text{mm}^2/\text{s}$); Vol= gray matter volume

Table 3
Group differences between patients with schizophrenia (SCZ) and healthy control individuals (HC) demonstrated by MANCOVAS

	Patients with chronic SCZ	Patients with early course SCZ
HFA	F=1.78, df1=4, df2=41, p=.15	F=5.50, df1=4, df2=26, p=.0020 *
FA	F=2.67, df1=4, df2=41, p=.046	F=2.83, df1=4, df2=28, p=.045
MD	F=.33, df1=4, df2=41, p=.86	F=3.02, df1=4, df2=26, p=.036
Volume	F=1.30, df1=4, df2=41, P=.29	F=2.04, df1=4, df2=26, p=.12

* indicates statistically significant correlation with $p < .013$ (Bonferroni Correction, $n=4$)
HFA= heterogeneity of fractional anisotropy; FA= fractional anisotropy; MD= mean diffusivity (in $10^{-3}\text{mm}^2/\text{s}$); Vol= gray matter volume

Table 4

Descriptive statistics (mean± standard deviation) of heterogeneity for patients with early course schizophrenia (SCZ) and healthy control individuals (HC)

	Patients with early course SCZ	HC
HFA frontal	.1190±.006474	.1113±.005676
HFA parietal	.1047±.005366	.1043±.005810
HFA temporal	.1140±.006606	.1148±.007776
HFA occipital	.09391±.004783	.09668±.007865

HFA= heterogeneity of fractional anisotropy