Psychiatry Research: Neuroimaging 231 (2015) 87–91

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Brief report

Fractional anisotropy in individuals with schizophrenia and their nonpsychotic siblings

Michael P. Harms [a,*], Kazi D. Akhter [b], John G. Csernansky [c], Susumu Mori [b], Deanna M. Barch [a,d]

[a] Department of Psychiatry, Washington University School of Medicine, St. Louis, MO, USA
[b] Department of Radiology and Radiological Science, The Johns Hopkins University School of Medicine, Baltimore, MD, USA
[c] Department of Psychiatry and Behavioral Sciences, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
[d] Department of Psychology, Washington University, St. Louis, MO, USA

ARTICLE INFO

Article history:
Received 21 February 2014
Received in revised form
18 August 2014
Accepted 9 October 2014
Available online 31 October 2014

Keywords:
Schizophrenia
Endophenotype
Diffusion tensor imaging (DTI)

ABSTRACT

Fractional anisotropy (FA) was examined in a priori selected fiber tracts in individuals with schizophrenia ($n=25$) and their non-psychotic siblings ($n=29$) versus controls ($n=35$). FA was reduced in a portion of the fornix in individuals with schizophrenia (although this did not survive correction for the number of tracts investigated). FA in the siblings did not differ from that in controls in any of the investigated tracts.

1. Introduction

Considerable interest exists in identifying heritable, quantitative biological markers that are associated with neurobiologically relevant dimensions of complex psychiatric disorders. Specific intermediate phenotypes ("endophenotypes") may be associated with a smaller number of genes than the overall psychiatric syndrome, translate better to animal models, and provide easily measured endpoints for studying the biological effects of treatments targeting specific molecular pathways (Gottesman and Gould, 2003; Braff et al., 2007). Further, validated endophenotypes are natural candidates for study as dimensions or constructs that may transcend individual psychiatric disorders in the effort to develop a new psychiatric nosology oriented around causative mechanisms instead of descriptive syndromes (Heckers, 2008; Craddock and Owen, 2010; Cuthbert and Insel, 2013).

Consistent with the frequent characterization of schizophrenia as a disorder of abnormal brain connectivity (Friston and Frith, 1995; Andreasen et al., 1999; Fornito et al., 2012), one such class of biological markers that has received considerable study in individuals with schizophrenia is white matter integrity assessed using diffusion tensor imaging (DTI). The most common DTI measure, fractional anisotropy (FA), is heritable (h^2 ~0.5 over the whole brain) (Kochunov et al., 2010; Skudlarski et al., 2013; Bohlken et al., 2014), thus satisfying that important characteristic of an endophenotype (Gottesman and Gould, 2003). A number of studies have reported decreased FA in various white matter tracts in individuals with schizophrenia, albeit with a mixture of both positive and negative findings across studies (for reviews, see Kanaan et al., 2005; Kubicki et al., 2007; Fitzsimmons et al., 2013). However, a much smaller number of studies have investigated FA in the siblings of family members with schizophrenia (Hoptman et al., 2008; Munoz Maniega et al., 2008; Camchong et al., 2009; Hao et al., 2009; Clark et al., 2011; Knochel et al., 2012a; Knochel et al., 2012b; Boos et al., 2013; Kubicki et al., 2013; Skudlarski et al., 2013). If FA is a candidate endophenotype related to a heritable genetic variation in schizophrenia, the non-psychotic siblings of individuals with schizophrenia should exhibit an intermediate degree of FA abnormality compared with their affected siblings. We present our findings regarding the integrity of a number of a priori selected white matter tracts in the siblings of individuals with schizophrenia. We hypothesized that individuals with schizophrenia (relative to controls) would exhibit decreased FA in at least several tracts and that their siblings would have an intermediate degree of FA reduction in those same tracts.

2. Methods

2.1. Subjects

The subjects were individuals who volunteered for studies of brain structure and function at Washington University School of Medicine in St. Louis, MO. Subjects

* Corresponding author. Tel.: +1 314 747 6173; fax: +1 314 747 2182.
E-mail address: mharms@wustl.edu (M.P. Harms).

http://dx.doi.org/10.1016/j.pscychresns.2014.10.009
0925-4927/

Table 1
Subject demographics and characteristics.

	SCZ[a] $n=25$	SCZ-SIB $n=29$	CON-SIB $n=17$	CON $n=18$	p[b]
Age (years)	24.2 (3.5)	24.2 (3.6)	20.3 (4.9)	21.4 (4.6)	0.003
Gender: *n* (%)					
Female	5 (20.0)	15 (51.7)	8 (47.1)	8 (44.4)	0.09
Male	20 (80.0)	14 (48.3)	9 (52.9)	10 (55.6)	
Race: *n* (%)					
Caucasian	15 (60.0)	15 (51.7)	8 (47.1)	9 (50.0)	0.75
African American	10 (40.0)	14 (48.3)	9 (52.9)	8 (44.4)	
Asian	0 (0)	0 (0)	0 (0)	1 (5.6)	
Education (years)	12.1 (1.8)	13.3 (2.2)	11.8 (3.9)	12.6 (3.2)	0.22
Parental education (years)	14.1 (2.1)	14.1 (2.3)	14.2 (1.3)	14.4 (1.6)	0.97
Crystallized IQ [c]	7.3 (2.8)	8.7 (3.0)	9.3 (3.0)	10.2 (2.7)	0.02
Lifetime histories [d]: *n* (%)					
Substance dependence	8 (32.0)	4 (13.8)	1 (7.1)	0 (0)	0.03
Mood disorder	9 (36.0)	9 (31.0)	1 (7.1)	0 (0)	0.007
Anxiety disorder	4 (16.0)	5 (17.2)	0 (0)	0 (0)	0.13
Total alcohol consumption in last 2 years (kg)	2.7 (6.0)	4.2 (5.7)	3.7 (6.0)	3.6 (5.7)	0.83
Cognitive domain scores [e]					
Working memory	−0.48 (0.69)	0.07 (0.59)	0.22 (0.41)	0.42 (0.66)	<0.0001
Episodic memory	−0.78 (0.66)	0.01 (0.67)	0.27 (0.66)	0.41 (0.76)	<0.0001
Executive function	−0.40 (0.90)	0.11 (0.48)	0.29 (0.51)	0.42 (0.59)	0.0004
Clinical symptom scores [e]					
Positive	1.07 (1.08)	−0.29 (0.28)	−0.30 (0.20)	−0.43 (0.21)	<0.0001
Negative	1.08 (0.78)	−0.06 (0.51)	−0.35 (0.22)	−0.37 (0.24)	<0.0001
Disorganization	0.73 (0.98)	−0.18 (0.31)	−0.25 (0.24)	−0.29 (0.32)	<0.0001

Values are mean (S.D.) unless stated otherwise.

[a] Mean duration of illness for SCZ was 5.2 years (S.D.=3.1).

[b] p-value for overall group effect using ANOVA for continuous variables and Fisher's exact test for categorical variables. Age and gender were included as covariates in the statistical analysis of FA.

[c] Scaled score on the vocabulary subtest of the Wechsler Adult Intelligence Scale (WAIS–III). In post-hoc testing, SCZ < CON-SIB ($p=0.03$) and SCZ < CON ($p=0.002$).

[d] Lifetime histories were assessed using DSM-IV criteria. For these histories, $n=14$ and 17 for CON-SIB and CON, respectively, due to missing data.

[e] *Z*-scores, computed from a battery of neuropsychological tests for the cognitive domain scores, and from the SANS/SAPS (Andreasen et al., 1995), SIPS (Miller et al., 1999), and Chapman Psychosis Proneness Scales (Chapman et al., 1995) for the clinical symptom scores. See Harms et al. (2007) for details. Posthoc testing indicated that SCZ scores differed from SCZ-SIB, CON-SIB, and CON for all 6 scores (all $p<0.005$). There were trend level ($0.05<p<0.10$) differences between SCZ-SIB and CON for the working memory ($p=0.06$) and episodic memory scores ($p=0.053$), and between SCZ-SIB and both CON-SIB and CON for negative symptoms ($p=0.08$ and 0.06, respectively). CON-SIB and CON did not differ for any of the 6 scores (all $p>0.3$).

comprised young individuals with DSM-IV schizophrenia (SCZ), their non-psychotic siblings (SCZ-SIB), healthy controls (CON), and their siblings (CON-SIB). There were 14 SCZ/SCZ-SIB pairs (28 subjects) and 12 CON/CON-SIB pairs (24 subjects) (and thus 37 singletons). Siblings were full siblings, based on self-report. The DTI data from this cohort have not been reported previously. The SCZ subjects were treated with antipsychotic medications (primarily atypical agents), and had been clinically stable for at least 2 weeks before study. SCZ-SIB, CON and CON-SIB subjects all had no lifetime history of any DSM-IV psychotic disorder, and the CON and CON-SIB had no first degree relatives with a psychotic disorder. Further details of exclusion criteria are available elsewhere (Harms et al., 2007; Mamah et al., 2008). See Table 1 for demographics and additional subject characteristics. All subjects gave written informed consent.

2.2. Imaging

Magnetic resonance scans were collected on a Siemens TimTrio 3 T using a 12-channel head coil. The DTI protocol included two whole-brain scans (each ~5 min) of a 30 gradient direction protocol ($b=800$ s/mm^2, TR/TE=8000/86 ms, Partial Fourier=6/8, iPAT/GRAPPA factor=2, Bandwidth=1396 Hz/Px), with five $b=0$ volumes interspersed through each scan. Voxel size was 2 mm isotropic.

2.3. Processing

DTI data were processed in a manner similar to the procedures of Faria et al. (2010) using the DTIStudio, ROIEditor, and DiffeoMap software packages. Raw diffusion-weighted images were co-registered and corrected for eddy currents and subject motion using a 12-parameter affine transform of the Automatic Image Registration (AIR) package. The diffusion tensor was calculated using multivariate linear fitting. The skull was stripped using the $b=0$ images (intensity thresholding followed by manual correction where necessary). For spatial normalization, $b=0$ images were first aligned to the ICBM-DTI-81 template using a 12-parameter affine transformation of AIR. After this initial alignment, more precise spatial normalization was performed using non-linear registration to a single subject atlas (JHU-DTI-MNI "Eve"), which has been extensively labeled (Mori et al., 2008; Oishi et al., 2009). This non-linear registration was performed using dual-contrast Large Deformation Diffeomorphic Metric Mapping, in which both $b=0$ and FA images were used to drive the registration (Ceritoglu et al., 2009). By applying the reverse transformation the labels (ROIs) in the "Eve" atlas were propagated back to each subject's native diffusion space, where FA was quantified for selected regions of interest (ROIs) (Table 2). Given the heterogeneity regarding which specific white matter tracts demonstrate FA changes in schizophrenia, we used an inclusive approach to ROI selection, including a tract if it had been implicated in several previous studies (for reviews, see Kanaan et al., 2005; Kubicki et al., 2007; Kyriakopoulos et al., 2008; White et al., 2008; Kyriakopoulos and Frangou, 2009; Peters et al., 2010; Melonakos et al., 2011; Fitzsimmons et al., 2013; for meta-analyses, see Ellison-Wright and Bullmore, 2009; Bora et al., 2011; Patel et al., 2011).

2.4. Statistical analysis

Group differences in FA were initially examined using a mixed model with group, hemisphere, group × hemisphere, gender and age as fixed effect predictors, with one random effect to account for familial covariance and another to model hemispheric covariance (using PROC MIXED of SAS 9.2). The group × hemisphere interaction was not significant for any of the investigated white matter tracts ($p>0.18$). Thus, we used a simpler mixed model with group, gender and age as fixed effect predictors and a single random effect to account for familial covariance. The dependent variable was the mean FA across hemispheres for each white matter tract (weighted by the number of voxels per hemisphere).[1] A common random variance was assumed to apply to both the SCZ/SCZ-SIB and CON/CON-SIB families.[2] The CON-SIB and CON subjects did not differ significantly in their

[1] Based on a report of decreases in axial diffusivity (AX) and mean diffusivity (MD) in individuals with increased familial risk for schizophrenia (Kubicki et al., 2013), as well as a report of increases in MD in unaffected relatives (Knochel et al., 2012b), we also conducted focused secondary analyses that compared whether SCZ-SIB and controls differed in AX or MD. These two groups did not differ in AX ($p>0.22$) or MD ($p>0.27$) for any of the investigated tracts.

[2] Very similar results were obtained when the two sets of siblings were allowed to each have a unique estimate of familial covariance. Also, very similar FA results were obtained using a subset of 76 subjects that were statistically matched on age across diagnostic groups.

Table 2
FA values by diagnostic group[a].

	SCZ	SCZ-SIB	Controls[b]
Anterior limb of the internal capsule (ALIC)	0.459 (5.26) [0.16]	0.466 (4.86) [0.55]	0.470 (5.35)
Cingulate portion of the cingulum (CGC)	0.368 (5.75) [0.18]	0.360 (5.14) [0.74]	0.358 (4.94)
Hippocampal portion of the cingulum (CGH)	0.361 (6.54) [0.97]	0.352 (5.90) [0.35]	0.360 (5.91)
Column and body portion of the fornix (FX)	0.315 (11.9) [0.09]	0.343 (10.8) [0.91]	0.344 (11.2)
Crus/stria terminalis portion of the fornix (FXcrus[c,d])	0.398 (5.56) [0.02]	0.413 (5.07) [0.54]	0.418 (5.30)
Inferior frontal-occipital fasciculus (IFO)	0.407 (6.22) [0.67]	0.401 (5.65) [0.80]	0.403 (5.81)
Superior longitudinal fasciculus (SLF)	0.409 (5.24) [0.96]	0.400 (4.85) [0.21]	0.410 (5.38)
Uncinate fasciculus (UNC)	0.287 (5.06) [0.75]	0.282 (4.51) [0.28]	0.289 (4.31)
Genu of the corpus callosum (GCC)	0.578 (4.90) [0.06]	0.588 (4.42) [0.62]	0.591 (4.47)
Splenium of the corpus callosum (SCC)	0.581 (6.68) [0.37]	0.585 (6.08) [0.62]	0.590 (6.31)

[a] Values in parentheses are standard error times 10^3. Brackets contain two-sided p-value in pairwise comparison vs. controls. p-values were not corrected for multiple comparisons.
[b] Combination of the CON-SIB and CON groups.
[c] Omnibus main-effect of group: $p=0.029$ ($F(2,25)=4.11$); $p=0.030$ for SCZ vs. SCZ-SIB; $p=0.016$ for SCZ vs. controls.
[d] The columns of the fornix are also known as the anterior pillars or fornicolumns, and are grouped together with the body of the fornix as a tract labeled "Fx" in the "Eve" atlas. The crus (crura) of the fornix are also known as the posterior pillars, and are not distinguishable from the stria terminalis in the region of the hippocampus at the imaging resolution of the current study. The tract that we call FXcrus in this paper is labeled "Fx/ST" in the "Eve" atlas. The mean (SD) bilateral volumes (mm^3) of these tracts in native subject space were: ALIC: 3589 (478); CGC: 8766 (1187); CGH: 2201 (268); FX: 590 (130); FXcrus: 2790 (306); IFO: 2733 (326); SLF: 13442 (2261); UNC: 597 (80); GCC: 5355 (901); SCC: 11289 (1746).

demographics, education, IQ, lifetime histories of Axis I psychopathology, or cognitive and clinical domain scores (Table 1). Therefore, to increase power and simplify data presentation, the model betas for those groups were averaged into a single "Control" group for comparison with SCZ and SCZ-SIB.[3] Group differences with a p-value <0.05 (uncorrected for multiple ROIs) are noted. (The Bonferroni corrected p-value threshold, controlling for the 10 ROIs would be 0.005, which was not satisfied for any comparison.). Correlations of clinical and cognitive measures with FA were not conducted given the generally negative nature of the overall findings regarding group differences in FA.

3. Results

The only tract that exhibited an effect of group on FA in an omnibus F-test comparing SCZ, SCZ-SIB and controls was FXcrus ($F(2,25)=4.11$, $p=0.029$; Table 2), which was the crus/stria terminalis portion of the fornix. Pairwise comparisons between groups of this tract revealed a statistically significant decrease of FA of 4–5% in SCZ compared with SCZ-SIB ($p=0.030$, Cohen's d effect size$=-0.46$) and controls ($p=0.016$, effect size$=-0.52$),[4] but no difference emerged between SCZ-SIB and controls ($p=0.54$).

4. Discussion

We found that FA in siblings of individuals with schizophrenia did not differ from FA in controls in any of the investigated white matter tracts. While most of the tracts investigated have been reported in at least one other study as differing in the family members of individuals with schizophrenia (vs. controls), the precise tracts implicated are highly divergent across studies. For every tract implicated in another familial study, an equal or greater number of other studies investigating the same tract or region have failed to find supporting results (Hoptman et al., 2008; Munoz Maniega et al., 2008; Camchong et al., 2009; Hao et al., 2009; Clark et al., 2011; Knochel et al., 2012a; Knochel et al., 2012b; Boos et al., 2013; Kubicki et al., 2013; Skudlarski et al., 2013). In that regard, our study adds an important additional set of data to what is currently still a small literature on FA in family members of individuals with schizophrenia. In particular, the current study is only the third in which the family members were restricted solely to siblings (cf. Boos et al., 2013; Hao et al., 2009), which yields a more homogenous sample as regards potential age and environmental confounds.

We found only marginal evidence for FA abnormalities in young individuals with schizophrenia. Namely, a 5% decrease in FA in FXcrus in SCZ relative to controls (effect size$=-0.52$) for which the p-value ($p=0.016$) would not survive correction for the number of investigated tracts. This result itself warrants caution, as the fornix is susceptible to partial volume artifacts with cerebral spinal fluid. Various reviews have noted the inconsistency and heterogeneity of DTI results in SCZ (Kanaan et al., 2005; Kyriakopoulos et al., 2008; White et al., 2008; Kyriakopoulos and Frangou, 2009; Peters et al., 2010; Melonakos et al., 2011). Notably, the sample size in the present study is comparable to (or larger than) those in many of the other studies that have reported FA reductions in various tracts in SCZ. In addition, the specific analytical approach used in this study has been validated and used successfully in other studies (Ceritoglu et al., 2009; Oishi et al., 2009; Faria et al., 2010; Faria et al., 2011). Nonetheless, it is possible that a different analytical approach, such as tract-based spatial statistics (TBSS; Smith et al., 2006) or automated tractography (e.g., TRACULA; Yendiki et al., 2011) might have revealed more group differences. Approaches that may be better equipped to handle heterogeneity in the location of white abnormalities across subjects (e.g., "pothole" approaches; White et al., 2013; Mayer et al., 2014) also warrant careful cross-methodological comparison and may provide a mechanism to relate different spatial profiles of abnormalities to differing disease subtypes. Another possibility for the negative findings in the current study is that FA decreases may have a progressive component (Rosenberger et al., 2008; Kochunov et al., 2013) and may be either absent or less robust in recent-onset schizophrenia. However, true longitudinal studies (in the same subjects) of FA in schizophrenia are needed, and the evidence for differential FA results between first episode and chronic schizophrenia is itself quite mixed (White et al., 2008; Kyriakopoulos and Frangou, 2009; Peters et al., 2010; Melonakos et al., 2011). Overall, the results of the current study are consistent with the idea that reported FA reductions in schizophrenia are more likely related to disease state than genetic risk for the disorder.

[3] Specifically, "CONTRAST" statements were used to compute statistics on linear combinations of the four subject groups in the model; e.g., the vector [−1 0 0.5 0.5] provided the difference ($½*(\beta_{CON}+\beta_{CON\text{-}SIB}) - \beta_{SCZ}$) and the vector [0 −1 0.5 0.5] provided the difference ($½*(\beta_{CON}+\beta_{CON\text{-}SIB}) - \beta_{SCZ\text{-}SIB}$). An F-test using both those contrast vectors provided an omnibus test for any difference between SCZ, SCZ-SIB, and "controls".
[4] Effect size computed as (t-value)/sqrt(d.f.) from the PROC MIXED model (d.f.=degrees of freedom).

Funding

This work was supported by the National Institute of Mental Health [MH071616, MH056584], the National Institute of Neurological Disorders and Stroke [NS084957], and the National Center for Research Resources [RR015241].

Contributors

J.G. Csernansky and D.M. Barch designed the study and obtained funding. K. Akhter and S. Mori performed the DTI analysis. M.P. Harms performed the statistical analysis, conducted the literature review, and wrote the first draft of the manuscript. All authors approved the final manuscript.

Acknowledgments

We thank the staff of the Administration/Assessment Core of the CCNMD at Washington University School of Medicine for collection of the clinical and imaging data.

References

Andreasen, N.C., Arndt, S., Alliger, R., Miller, D., Flaum, M., 1995. Symptoms of schizophrenia. Methods, meanings, and mechanisms. Archives of General Psychiatry 52, 341–351.

Andreasen, N.C., Nopoulos, P., O'Leary, D.S., Miller, D.D., Wassink, T., Flaum, M., 1999. Defining the phenotype of schizophrenia: cognitive dysmetria and its neural mechanisms. Biological Psychiatry 46, 908–920.

Bohlken, M.M., Mandl, R.C., Brouwer, R.M., van den Heuvel, M.P., Hedman, A.M., Kahn, R.S., Hulshoff Pol, H.E., 2014. Heritability of structural brain network topology: a DTI study of 156 twins. Human Brain Mapping 35 (10), 5295–5305.

Boos, H.B., Mandl, R.C., van Haren, N.E., Cahn, W., van Baal, G.C., Kahn, R.S., Hulshoff Pol, H.E., 2013. Tract-based diffusion tensor imaging in patients with schizophrenia and their non-psychotic siblings. European Neuropsychopharmacology 23, 295–304.

Bora, E., Fornito, A., Radua, J., Walterfang, M., Seal, M., Wood, S.J., Yucel, M., Velakoulis, D., Pantelis, C., 2011. Neuroanatomical abnormalities in schizophrenia: a multimodal voxelwise meta-analysis and meta-regression analysis. Schizophrenia Research 127, 46–57.

Braff, D.L., Freedman, R., Schork, N.J., GottesmanII, N.J., 2007. Deconstructing schizophrenia: an overview of the use of endophenotypes in order to understand a complex disorder. Schizophrenia Bulletin 33, 21–32.

Camchong, J., Lim, K.O., Sponheim, S.R., Macdonald, A.W., 2009. Frontal white matter integrity as an endophenotype for schizophrenia: diffusion tensor imaging in monozygotic twins and patients' nonpsychotic relatives. Frontiers in Human Neuroscience 3, 35.

Ceritoglu, C., Oishi, K., Li, X., Chou, M.C., Younes, L., Albert, M., Lyketsos, C., van Zijl, P.C., Miller, M.I., Mori, S., 2009. Multi-contrast large deformation diffeomorphic metric mapping for diffusion tensor imaging. Neuroimage 47, 618–627.

Chapman, J.P., Chapman, L.J., Kwapil, T.R., 1995. Scales for the measurement of schizotypy. In: Raine, T., Lencz, T., Mednick, S. (Eds.), Schizotypal Personality. Cambridge University Press, New York, pp. 79–106.

Clark, K.A., Nuechterlein, K.H., Asarnow, R.F., Hamilton, L.S., Phillips, O.R., Hageman, N.S., Woods, R.P., Alger, J.R., Toga, A.W., Narr, K.L., 2011. Mean diffusivity and fractional anisotropy as indicators of disease and genetic liability to schizophrenia. Journal of Psychiatric Research 45, 980–988.

Craddock, N., Owen, M.J., 2010. The Kraepelinian dichotomy – going, going… but still not gone. British Journal of Psychiatry 196, 92–95.

Cuthbert, B.N., Insel, T.R., 2013. Toward the future of psychiatric diagnosis: the seven pillars of RDoC. BMC Medicine 11, 126.

Ellison-Wright, I., Bullmore, E., 2009. Meta-analysis of diffusion tensor imaging studies in schizophrenia. Schizophrenia Research 108, 3–10.

Faria, A.V., Hoon, A., Stashinko, E., Li, X., Jiang, H., Mashayekh, A., Akhter, K., Hsu, J., Oishi, K., Zhang, J., Miller, M.I., van Zijl, P.C., Mori, S., 2011. Quantitative analysis of brain pathology based on MRI and brain atlases–applications for cerebral palsy. Neuroimage 54, 1854–1861.

Faria, A.V., Zhang, J., Oishi, K., Li, X., Jiang, H., Akhter, K., Hermoye, L., Lee, S.K., Hoon, A., Stashinko, E., Miller, M.I., van Zijl, P.C., Mori, S., 2010. Atlas-based analysis of neurodevelopment from infancy to adulthood using diffusion tensor imaging and applications for automated abnormality detection. Neuroimage 52, 415–428.

Fitzsimmons, J., Kubicki, M., Shenton, M.E., 2013. Review of functional and anatomical brain connectivity findings in schizophrenia. Current Opinion in Psychiatry 26, 172–187.

Fornito, A., Zalesky, A., Pantelis, C., Bullmore, E.T., 2012. Schizophrenia, neuroimaging and connectomics. Neuroimage 62, 2296–2314.

Friston, K.J., Frith, C.D., 1995. Schizophrenia: a disconnection syndrome? Clinical Neuroscience 3, 89–97.

Gottesman, I.I., Gould, T.D., 2003. The endophenotype concept in psychiatry: etymology and strategic intentions. American Journal of Psychiatry 160, 636–645.

Hao, Y., Yan, Q., Liu, H., Xu, L., Xue, Z., Song, X., Kaneko, Y., Jiang, T., Liu, Z., Shan, B., 2009. Schizophrenia patients and their healthy siblings share disruption of white matter integrity in the left prefrontal cortex and the hippocampus but not the anterior cingulate cortex. Schizophrenia Research 114, 128–135.

Harms, M.P., Wang, L., Mamah, D., Barch, D.M., Thompson, P.A., Csernansky, J.G., 2007. Thalamic shape abnormalities in individuals with schizophrenia and their nonpsychotic siblings. Journal of Neuroscience 27, 13835–13842.

Heckers, S., 2008. Making progress in schizophrenia research. Schizophrenia Bulletin 34, 591–594.

Hoptman, M.J., Nierenberg, J., Bertisch, H.C., Catalano, D., Ardekani, B.A., Branch, C.A., Delisi, L.E., 2008. A DTI study of white matter microstructure in individuals at high genetic risk for schizophrenia. Schizophrenia Research 106, 115–124.

Kanaan, R.A., Kim, J.S., Kaufmann, W.E., Pearlson, G.D., Barker, G.J., McGuire, P.K., 2005. Diffusion tensor imaging in schizophrenia. Biological Psychiatry 58, 921–929.

Knochel, C., O'Dwyer, L., Alves, G., Reinke, B., Magerkurth, J., Rotarska-Jagiela, A., Prvulovic, D., Hampel, H., Linden, D.E., Oertel-Knochel, V., 2012a. Association between white matter fiber integrity and subclinical psychotic symptoms in schizophrenia patients and unaffected relatives. Schizophrenia Research 140, 129–135.

Knochel, C., Oertel-Knochel, V., Schonmeyer, R., Rotarska-Jagiela, A., van de Ven, V., Prvulovic, D., Haenschel, C., Uhlhaas, P., Pantel, J., Hampel, H., Linden, D.E., 2012b. Interhemispheric hypoconnectivity in schizophrenia: fiber integrity and volume differences of the corpus callosum in patients and unaffected relatives. Neuroimage 59, 926–934.

Kochunov, P., Glahn, D.C., Lancaster, J.L., Winkler, A.M., Smith, S., Thompson, P.M., Almasy, L., Duggirala, R., Fox, P.T., Blangero, J., 2010. Genetics of microstructure of cerebral white matter using diffusion tensor imaging. Neuroimage 53, 1109–1116.

Kochunov, P., Glahn, D.C., Rowland, L.M., Olvera, R.L., Winkler, A., Yang, Y.H., Sampath, H., Carpenter, W.T., Duggirala, R., Curran, J., Blangero, J., Hong, L.E., 2013. Testing the hypothesis of accelerated cerebral white matter aging in schizophrenia and major depression. Biological Psychiatry 73, 482–491.

Kubicki, M., McCarley, R., Westin, C.F., Park, H.J., Maier, S., Kikinis, R., Jolesz, F.A., Shenton, M.E., 2007. A review of diffusion tensor imaging studies in schizophrenia. Journal of Psychiatric Research 41, 15–30.

Kubicki, M., Shenton, M.E., Maciejewski, P.K., Pelavin, P.E., Hawley, K.J., Ballinger, T., Swisher, T., Jabbar, G.A., Thermenos, H.W., Keshavan, M.S., Seidman, L.J., Delisi, L.E., 2013. Decreased axial diffusivity within language connections: a possible biomarker of schizophrenia risk. Schizophrenia Research 148, 67–73.

Kyriakopoulos, M., Bargiotas, T., Barker, G.J., Frangou, S., 2008. Diffusion tensor imaging in schizophrenia. European Psychiatry 23, 255–273.

Kyriakopoulos, M., Frangou, S., 2009. Recent diffusion tensor imaging findings in early stages of schizophrenia. Current Opinion in Psychiatry 22, 168–176.

Mamah, D., Harms, M.P., Wang, L., Barch, D., Thompson, P., Kim, J., Miller, M.I., Csernansky, J.G., 2008. Basal ganglia shape abnormalities in the unaffected siblings of schizophrenia patients. Biological Psychiatry 64, 111–120.

Mayer, A.R., Bedrick, E.J., Ling, J.M., Toulouse, T., Dodd, A., 2014. Methods for identifying subject-specific abnormalities in neuroimaging data. Human Brain Mapping 35, 5457–5470.

Melonakos, E.D., Shenton, M.E., Rathi, Y., Terry, D.P., Bouix, S., Kubicki, M., 2011. Voxel-based morphometry (VBM) studies in schizophrenia-can white matter changes be reliably detected with VBM? Psychiatry Research: Neuroimaging 193, 65–70.

Miller, T.J., McGlashan, T.H., Woods, S.W., Stein, K., Driesen, N., Corcoran, C.M., Hoffman, R., Davidson, L., 1999. Symptom assessment in schizophrenic prodromal states. Psychiatric Quarterly 70, 273–287.

Mori, S., Oishi, K., Jiang, H., Jiang, L., Li, X., Akhter, K., Hua, K., Faria, A.V., Mahmood, A., Woods, R., Toga, A.W., Pike, G.B., Neto, P.R., Evans, A., Zhang, J., Huang, H., Miller, M.I., van Zijl, P., Mazziotta, J., 2008. Stereotaxic white matter atlas based on diffusion tensor imaging in an ICBM template. Neuroimage 40, 570–582.

Munoz Maniega, S., Lymer, G.K., Bastin, M.E., Marjoram, D., Job, D.E., Moorhead, T.W., Owens, D.G., Johnstone, E.C., McIntosh, A.M., Lawrie, S.M., 2008. A diffusion tensor MRI study of white matter integrity in subjects at high genetic risk of schizophrenia. Schizophrenia Research 106, 132–139.

Oishi, K., Faria, A., Jiang, H., Li, X., Akhter, K., Zhang, J., Hsu, J.T., Miller, M.I., van Zijl, P.C., Albert, M., Lyketsos, C.G., Woods, R., Toga, A.W., Pike, G.B., Rosa-Neto, P., Evans, A., Mazziotta, J., Mori, S., 2009. Atlas-based whole brain white matter analysis using large deformation diffeomorphic metric mapping: application to normal elderly and Alzheimer's disease participants. Neuroimage 46, 486–499.

Patel, S., Mahon, K., Wellington, R., Zhang, J., Chaplin, W., Szeszko, P.R., 2011. A meta-analysis of diffusion tensor imaging studies of the corpus callosum in schizophrenia. Schizophrenia Research 129, 149–155.

Peters, B.D., Blaas, J., de Haan, L, 2010. Diffusion tensor imaging in the early phase of schizophrenia: what have we learned? Journal of Psychiatric Research 44, 993–1004.

Rosenberger, G., Kubicki, M., Nestor, P.G., Connor, E., Bushell, G.B., Markant, D., Niznikiewicz, M., Westin, C.F., Kikinis, R., A, J.S., McCarley, R.W., Shenton, M.E., 2008. Age-related deficits in fronto-temporal connections in schizophrenia: a diffusion tensor imaging study. Schizophrenia Research 102, 181–188.

Skudlarski, P., Schretlen, D.J., Thaker, G.K., Stevens, M.C., Keshavan, M.S., Sweeney, J.A., Tamminga, C.A., Clementz, B.A., O'Neil, K., Pearlson, G.D., 2013. Diffusion tensor

imaging white matter endophenotypes in patients with schizophrenia or psychotic bipolar disorder and their relatives. American Journal of Psychiatry 170, 886–898.
Smith, S.M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T.E., Mackay, C.E., Watkins, K.E., Ciccarelli, O., Cader, M.Z., Matthews, P.M., Behrens, T.E., 2006. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. Neuroimage 31, 1487–1505.
White, T., Ehrlich, S., Ho, B.C., Manoach, D.S., Caprihan, A., Schulz, S.C., Andreasen, N.C., Gollub, R.L., Calhoun, V.D., Magnotta, V.A., 2013. Spatial characteristics of white matter abnormalities in schizophrenia. Schizophrenia Bulletin 39, 1077–1086.
White, T., Nelson, M., Lim, K.O., 2008. Diffusion tensor imaging in psychiatric disorders. Topics in Magnetic Resonance Imaging 19, 97–109.
Yendiki, A., Panneck, P., Srinivasan, P., Stevens, A., Zollei, L., Augustinack, J., Wang, R., Salat, D., Ehrlich, S., Behrens, T., Jbabdi, S., Gollub, R., Fischl, B., 2011. Automated probabilistic reconstruction of white-matter pathways in health and disease using an atlas of the underlying anatomy. Frontiers in Neuroinformatics 5, 23.