Sexual Dimorphic Abnormalities in White Matter Geometry Common to Schizophrenia and Non-Psychotic High-Risk Subjects: Evidence for a Neurodevelopmental Risk Marker?

Peter Savadjiev,¹ Larry J. Seidman,^{2,3} Heidi Thermenos,^{2,3}
Matcheri Keshavan,³ Susan Whitfield-Gabrieli,⁴ Tim J. Crow,⁵ and
Marek Kubicki^{1,6*}

¹Department of Psychiatry, Brigham and Women's Hospital, and Harvard Medical School, Boston, Massachusetts

²Massachusetts Mental Health Center, Division of Public Psychiatry, Boston, Massachusetts

³Department of Psychiatry, Beth Israel Deaconess Medical Center, Boston, Massachusetts

⁴Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, Massachusetts

⁵SANE POWIC, University Department of Psychiatry, Warneford Hospital, Oxford, United Kingdom

⁶Department of Psychiatry and Radiology, Brigham and Women's Hospital, and Harvard Medical School, Boston, Massachusetts

Abstract: The characterization of neurodevelopmental aspects of brain alterations require neuroimaging methods that reflect correlates of neurodevelopment, while being robust to other progressive pathological processes. Newly developed neuroimaging methods for measuring geometrical features of the white matter fall exactly into this category. Our recent work shows that such features, measured in the anterior corpus callosum in diffusion MRI data, correlate with psychosis symptoms in patients with adolescent onset schizophrenia and subside a reversal of normal sexual dimorphism. Here, we test the hypothesis that similar developmental deviations will also be present in nonpsychotic subjects at familial high risk (FHR) for schizophrenia, due to genetic predispositions. Demonstrating such changes would provide a strong indication of neurodevelopmental deviation extant before, and independent of pathological changes occurring after disease onset. We examined the macrostructural geometry of corpus callosum white matter in diffusion MRI data of 35 non-psychotic subjects with genetic (familial) risk for schizophrenia, and 26 control subjects, both male and female. We report a reversal of normal sexual dimorphism in callosal white matter geometry consistent with recent results in adolescent onset

Contract grant sponsor: National Institutes of Health; Contract grant numbers: R01 AG04252, R01 MH102377, R21 MH083205, R01 MH64023; Contract grant sponsor: NARSAD Young Investigator Award (Brain and Behavior Research Foundation); Contract grant number: 22591.

*Correspondence to: Marek Kubicki, MD, PhD, Psychiatry Neuroimaging Laboratory, Department of Psychiatry, Brigham and

Women's Hospital, Harvard Medical School, 1249 Boylston Street, Boston, MA 02215. E-mail: kubicki@bwh.harvard.edu

Received for publication 22 July 2015; Revised 30 September 2015; Accepted 4 October 2015.

DOI: 10.1002/hbm.23026

Published online 15 October 2015 in Wiley Online Library (wileyonlinelibrary.com).

schizophrenia. This pattern may be indicative of an error in neurogenesis and a possible trait marker of schizophrenia. *Hum Brain Mapp* 37:254–261, 2016. © 2015 Wiley Periodicals, Inc.

Key words: white matter geometry; sexual dimorphism; neurodevelopment; familial risk; schizophrenia

INTRODUCTION

Schizophrenia is a chronic, debilitating disease, affecting close to 1% of the world's population. The etiopathology of schizophrenia is still not well understood. However, evidence suggests several neurodevelopmental anomalies that might affect maturational trajectories [Lewis and Levitt, 2002], as well as neurodegenerative abnormalities, leading to cognitive impairments along the schizophrenia spectrum. It is now also apparent that deficits in schizophrenia involve not just gray matter, but also white matter [Kubicki et al., 2007], perhaps even to a greater degree [Lewis, 2011]. Recent developments in diffusion MRI (dMRI), a method sensitive to white matter pathology, suggest that white matter pathology exists at every stage along the time-course of schizophrenia, and likely also prior to its onset [Kubicki et al., 2007; Peters et al., 2010]. dMRI, however, similar to volumetric MRI, has no biological specificity to underlying micropathology. Thus, white matter changes (related to brain development), vs. those related to inflammation and/or demyelination, cannot currently be differentiated, as they both might affect standard diffusion measures in the same nonspecific way. Consequently, changes in Fractional Anisotropy (FA, the most popular measure derived from dMRI) follow a wide variety of other nonspecific neuroimaging findings in schizophrenia and schizophrenia risk, including gray matter volume decrease, cortical thinning, and functional connectivity abnormalities [Fitzsimmons et al., 2013; Thermenos et al., 2013]. As all of these measures undergo normal maturational trajectories and change as a function of aging, it is important to employ noninvasive measures that can distinguish between neurodevelopment and other neuropathological processes.

For example, recently published studies suggest that cortical geometry (e.g., the cortical folding pattern), a brain feature that develops very early during ontogenesis, is relatively stable in brain maturation and can be considered a feature reflective of neurodevelopmental processes, as opposed to progressive neuropathological processes [e.g., Pantelis et al., 2003]. It has also been demonstrated that the sulco-gyral pattern develops *in utero* [e.g., Armstrong et al., 1995; Goldman-Rakic and Rakic, 1984; Rajagopalan et al., 2011] and thus any differences between groups reflects a prenatal sign of a later developing disorder. In fact abnormal cortical folding within the prefrontal regions has been suggested as a potential predictor for the development of schizophrenia in at risk individuals [Harris

et al., 2007]. However, the drawback of cortical folding as a neuroimaging measure is the large anatomical variability among individuals, and the lack of precise mapping of the local sulco-gyral pattern in the normal brain.

At the same time, the value of the morphology of white matter connections as an index of neurodevelopment has been underexplored. It has long been recognized that, during gestation, the development of cortical folding is influenced by axonal (white matter) connections [Dehay et al., 1996; Goldman-Rakic, 1980]. White matter connections not only provide connectivity within the brain, but also form a skeleton, which is much less variable than the pattern of cortical folding. It is thus conceivable that changes of geometric nature within the white matter skeleton might reflect abnormal brain development in schizophrenia in a manner that is more robust and reliable than changes in cortical folding. Consistent with this view are our earlier findings in patients with chronic schizophrenia [Whitford et al., 2011], which demonstrate abnormalities in the macrostructural geometry of interhemispheric white matter tracts connecting the left and right frontal lobes via the genu of the corpus callosum. More recently, we showed that geometric abnormalities in the anterior corpus callosum in adolescent onset schizophrenia are sexually dimorphic [Savadjev et al., 2014a]. Of note, sex differences are characteristic of schizophrenia (i.e., its age of onset differs between the sexes, occurring on average 2 years earlier in life and with generally worse outcomes in males than in females [e.g., Taylor, 2003]). Sexual dimorphism has also been associated with brain pathology, more specifically to alterations in the sulco-gyral pattern of the orbital frontal cortices [Uehara-Aoyama et al., 2011], and in tracts interconnecting these structures [Crow et al., 2007] in schizophrenia. Sexual dimorphic changes in brain volumes have also been associated with familial schizophrenia risk [Goldstein et al., 2007], but have not been studied in association with brain geometry and architecture.

Here we extend our previous work in an important new direction: we test the hypothesis that a developmental deviation in brain growth affecting the geometry of corpus callosal fibers interconnecting frontal regions will be present not only in diagnosed patients, but also in nonpsychotic subjects at familial high risk for schizophrenia. Demonstrating sex-specific changes in such subjects would provide a strong indication of neurodevelopmental pathology extant before, and independent of neurodegenerative changes occurring after disease onset. We predict that subjects at familial high risk (FHR) for schizophrenia will

share with diagnosed patients a similar developmental phenotype of deviations in callosal fiber geometry. Thus our hypothesis directs attention to callosal fiber geometry as an imaging marker for schizophrenia risk.

MATERIALS AND METHODS

Measuring White Matter Geometry With DTI

Early in the history of DTI, it was proposed that in addition to what can be learned from measures of individual diffusion tensor properties, such as FA, the information found in *patterns* of tensors and their differential structure may provide further insights into tissue organization, structure, and function [Basser, 1997]. Today, however, most clinical applications of DTI are still focused on single-tensor measures such as FA. To break from this convention, Savadjiev et al. [2010] introduced novel methods for white matter geometry estimation. Consistent with the idea of identifying new tissue properties from the differential structure of the diffusion tensor field [Basser, 1997], the measures introduced by Savadjiev et al. [2010] are tuned to isolate geometrical information based on the variation in tensor orientation within a neighborhood of voxels. Specifically, the index of “shape normalized dispersion” (SHD) measures the extent to which the fibers deviate from being parallel, e.g., in the case of a fanning. This measure is based on a mathematical framework that computes local variation in tensor orientation, from the gradient of the diffusion tensor field. For all mathematical details, please refer to Savadjiev et al. [2010].

This approach to computing white matter geometry is in contrast to the vast majority of other methods for white matter geometry computation. Such methods typically first compute fiber trajectories with a tractography algorithm, and then compute the geometry of these trajectories. However, all such tractography-based methods are inherently limited in stability and reproducibility. Because it computes geometry information directly from the diffusion tensor volumes, the SHD measure of Savadjiev et al. [2010] has the advantage to bypass the need for tractography, and is thus immune to the limitations of tractography algorithms. For a discussion and comparison of tensor-based approach to white matter geometry, such as provided by the SHD measure, and a tractography based approach, please refer to Savadjiev et al. [2014b].

Thus, in order to benefit from the advantages provided by the SHD measure, and to follow the work of Whitford et al. [2011] and Savadjiev et al. [2014a], in the present article we also adopt the SHD measure. For simplicity and clarity, in this article we will refer to it simply as “dispersion.”

Even though the computation of this dispersion measure is completely independent of tractography, for visualization purposes it is helpful to run tractography and to color the resulting fiber tracts with the precomputed dispersion

Figure 1.

Callosal fibers of the Genu in a single subject, colored by their dispersion index using a heat colormap, such that red color indicates higher dispersion. The tractography in this figure is shown for visualization only; as explained in the text, the computation of the SHD dispersion measure is performed directly from the diffusion tensor field and is completely independent of tractography.

values. Thus, to provide an illustration, we computed the dispersion measure in one subject, and then color-mapped its values onto a set of fiber tracts passing through the genu of the corpus callosum, as shown in Figure 1.

Subjects

Thirty-five FHR subjects (9 males and 26 females) were recruited from the Boston Area community, partially by advertisements within chapters of The National Alliance on Mental Illness (NAMI), mean age: 25.7 years, standard dev.: 3.4 years, range: 19–32 years. Inclusion criteria included: ages between 18 and 32 years, at least two relatives with a psychiatric illness, with at least one first-degree relative with a confirmed diagnosis of schizophrenia or schizoaffective disorder. Twenty six controls with very low risk for schizophrenia (NCs; 10 males and 16 females) participated in the study, with mean age: 24.3 years, standard dev.: 2.8 years, range: 20–30 years. Controls were matched to FHR subjects on age, sex, and ethnicity and recruited by advertisement in the same communities. The following exclusion criteria were used for controls: a family history of schizophrenia, schizoaffective disorder, bipolar disorder, any psychotic disorder, or suicide in a 1st, 2nd, or 3rd degree relative, history of any psychotic diagnosis or treatment with antipsychotic medication, or meeting criteria for a prodromal syndrome according to the criteria of prodrome syndromes (COPS).

For all subjects, The Diagnostic Interview for Genetic Studies (DIGS; http://www.nimhgenetics.org/interviews/digs_4.0_bp) was used to determine lifetime presence of

Axis I or II psychiatric disorder and/or substance use (none of the subjects were diagnosed with past substance abuse, however use of marijuana and alcohol in the past were not considered exclusion criteria). The interviews were performed in combination with the SIS (Structured Interview for Schizotypy). Premorbid (pre-prodromal) function was assessed using the Premorbid Adjustment Scale (Cannon-Spoor et al., 1982). A medical history was also taken and included history of medication. Nearly 22 out of 35 FHR subjects and two out of 26 NC subjects were given a clinical diagnosis, as summarized in Table I.

Hand preference was assessed using the 23 item Annett scale [Annett, 1985]. Because of language lateralization, and reported differences in diffusion indices between left and right-handed individuals [Catani and Mesulam, 2008], left-handed subjects were excluded from the study. Written informed consent was obtained prior to study participation. The research protocol was approved by VABHS-spell out, Beth Israel Deaconess Medical Center, Massachusetts Institute of Technology, and Harvard Medical School IRBs.

Data Acquisition

Diffusion weighted magnetic resonance images (DW-MRI) were acquired on a Siemens TIM TRIO 3T research dedicated full-body scanner at Massachusetts Institute of Technology, equipped with a 40 mT m⁻¹ gradient set. DTI scans were acquired using an echo planar imaging (EPI) DTI Tensor sequence. A 32 Channel coil and parallel imaging using GRAPPA with speed-up factor of 2 was used. We used the scanning protocol established for Boston CIDAR (Center for Intervention Development and Applied Research), in which we acquired 60 directions with $b = 700$ s mm⁻², 10 baseline scans with $b = 0$ s mm⁻². The following scanning parameters were used: TR 8,000 ms, TE 84 ms, FOV 25.6 cm, 128 × 128 encoding steps, and 2-mm slice thickness (thus resulting in 2 × 2 × 2 mm³ voxel size), 64 axial slices were covering the whole brain. Total scan time for this sequence was 10 min. While it is common to work with b values higher than 700 s mm⁻² on 3T scanners, here we work with a sequence that prioritizes higher SNR, as opposed to higher diffusion weighting.

Diffusion Image Processing

In our experiments, we compare white matter geometry of male and female brains, controls, and FHR subjects. It is known that male brains are on average bigger than female brains. It is also possible that an overall brain size difference exists between controls and FHR subjects. To ensure that observed differences in white matter geometry are not driven by differences in overall brain size, we performed a uniform scaling of all DW-MRI volumes, such that the resulting volumes have the same overall size. This is achieved via affine registration, with no deformations

TABLE I. Data for subset of subjects (22 FHR subjects out of a total of 35 FHR subjects, 2 NC subjects out of a total of 26) that have been diagnosed with depression, anxiety and/or other mood or psychiatric disorders

Sex	Diagnosis	Prodromal	Group (1 = Con 2 = at risk)
F	Depression, schizotypal traits	No	2
F	Schizotypal traits	No	2
F	Depression	No	2
F	Depression, anxiety	No	2
F	Depression	No	2
F	Depression, anxiety	No	2
F	Depression, schizotypal traits	No	2
F	Depression	No	2
F	Anxiety	No	2
F	Depression, anxiety	No	2
F	Depression	No	2
F	Schizotypal traits, depression	No	2
F	Depression	No	2
F	Depression, schizotypal traits	No	2
F	Depression, anxiety, schizotypal traits	Yes	2
F	Schizotypal traits, depression	Yes	2
M	Depression	No	2
M	Depression	No	2
M	Schizotypal traits	No	2
M	Depression	No	2
M	Anxiety	No	2
M	Depression	Yes	2
F	Depression	No	1
F	Depression	No	1

Each row corresponds to one subject.

other than uniform scaling, using the flirt software (fsl.fmrib.ox.ac.uk). In doing so, we are also following the methodology of Savadjiev et al. [2014a].

Prior to tensor estimation from the DW-MRI data, DICOM images were converted to nrrd format, and data were corrected for eddy current and motion artifacts, using in-house software. However, potential susceptibility artifacts such as EPI distortion were not corrected. Tensors were estimated using the Least Squares method [Tristán-Vega et al., 2012] and the 3DSlicer software version 3.6.4 (www.slicer.org). Following tensor estimation, the SHD measure was computed at each voxel as described by Savadjiev et al. [2010].

Tract-Based Spatial Statistics

Our analysis is based on the Tract-Based Spatial Statistics method [TBSS; Smith et al., 2006], where white matter tracts are abstracted as a set of locations of locally maximal FA that are then connected to form a white matter skeleton. TBSS proceeds by first aligning all subjects' FA and dispersion images to a common space using the

nonlinear registration tool FNIRT (FMRIB Centre, University of Oxford; www.fmrib.ox.ac.uk/analysis/techrep). This nonrigid step refines the initial affine registration with uniform scaling described above. The aligned FA images are then averaged to create a mean FA image, which is then thinned to create the mean FA skeleton (thresholded at an FA value of 0.35). The skeleton represents the centers of all white matter tracts common to all subjects, and each subject's dispersion data is projected onto it. To achieve this, for each skeleton voxel in each subject, a search is made for the maximum FA value in the direction perpendicular to the local skeleton structure. This location defines the local tract center and is recorded. Each subject's (aligned) FA and dispersion data at these locations was then projected onto the skeleton, and the resulting data was used to perform statistics between subjects.

Statistics

We performed two types of statistical analysis. In the first set of experiments, we performed the standard statistical analysis typically done in the TBSS framework. This was done via permutation testing, using the randomize tool, part of FSL software library. For details on permutation testing in neuroimaging, see Nichols and Holmes [2002]. The randomize tool implements permutation testing within a standard Generalized Linear Model (GLM) framework. Clusters in the data are enhanced via the Threshold-Free Cluster Enhancement (TFCE) method [Smith and Nichols, 2009], which allows the use of spatial neighborhood information to increase confidence in statistical differences over groups of neighboring voxels, without requiring an *a priori* threshold for cluster definition. The *P* value for each cluster is then corrected by controlling for the family-wise error rate. Multiple comparison correction is thus performed by accounting for the entire extent of the white matter skeleton.

In the second set of experiments, instead of searching for locations on the skeleton that exhibit a group difference, we first isolated that part of the skeleton that corresponds to the genu of the corpus callosum. To do so, we simply masked the whole brain skeleton with the corresponding ROI from the Johns Hopkins University atlas, which is part of FSL. Both the skeleton and the atlas are defined in standard MNI space, which facilitates the atlas-based masking of the skeleton. Then, for each subject, we averaged the projected data on the skeleton over the Genu ROI, in order to obtain one average measure of dispersion per subject. We then used these averages in order to determine a Diagnosis X Sex interaction over the Genu ROI.

RESULTS

The standard TBSS experiment, described in the Methods section, is designed to reveal group differences in

Figure 2.

Significant Group $\times$ Sex interaction ($P = 0.0387$) with the dispersion measure within the Genu ROI in the corpus callosum.

localized areas along the skeleton. In the present study, the method failed to reveal significant local differences either in FA or in the dispersion measure. However, since our hypothesis points specifically to the corpus callosum (the genu, where our previous two studies demonstrated group differences), we performed an alternative analysis, whereby we isolated that part of the skeleton that corresponds to the genu, using the Johns Hopkins University ICBM-DTI-81 atlas. Following the TBSS projection step onto the skeleton [Smith et al., 2006], we averaged the projected dispersion values over that part of the skeleton, and performed an analysis using these average values.

This experiment revealed significant group $\times$ sex interaction ($P = 0.0387$) with the dispersion measure (Fig. 2). Thus, the normal sexual dimorphism observed in the control population is reversed in the high-risk subjects. In the normal population, females have a higher degree of dispersion than males. In the high-risk population, it is males that have a higher degree of dispersion. Post-hoc *t* tests revealed a pattern of differences (Fig. 3) that resembles those observed previously by us in adolescent onset schizophrenia patients [Savadjiev et al., 2014a]. In comparison, FA showed no Group $\times$ Sex interaction: $P = 0.4283$.

Thus, our experiment with the dispersion measure reveals a reversal in the normal sexual dimorphism, as evidenced by the significant Group $\times$ Sex interaction. As reported in Figures 2 and 3, the mean difference between males and females goes in the opposite direction in the control group compared to the high-risk population. However, while the post-hoc *t* test between males and females in the control group is borderline significant, the same comparison in the high-risk population is not. This could be due to the relatively small population sample used in this study, as discussed further in the next section. Because of the small population size, our results remain

Figure 3.

Figure showing the result of post-hoc *t* tests between male controls (MC), female controls (FC), male familial high risk subjects (MFHR), and female familial high risk subjects (FFHR). These results reveal a pattern of reversal of normal sexual dimorphism in high risk subjects, similar to the one observed in figure 4 in Savadjiev et al. [2014a] in adolescent onset schizophrenia. The mean dispersion value for each group is indicated next to its name. The prominence of the font is a visual indication of the magnitude of mean dispersion in that group. The arrows denote comparisons between groups, such that the arrow points in the direction of decreasing mean dispersion. The *P* values for each comparison are indicated next to each arrow.

preliminary. Nevertheless, this is the first study to replicate in high-risk subjects white matter geometry abnormalities previously reported in schizophrenia subjects. As such, it underscores the value of working with a measure specific to a particular feature of the white matter (in our case, the geometrical notion of dispersion), in order to isolate a particular effect, as opposed to using nonspecific DTI diffusivity measures such as FA.

DISCUSSION

White matter pathology, as measured with DTI, has been reported in all phases of schizophrenia, as well as before its onset. A majority of these reports of white matter changes are measured with FA. However, the specificity of FA to white matter integrity has not been confirmed [Jones et al., 2013]. Our previous work demonstrated that dispersion partially explains FA abnormalities in the corpus callosum in chronic schizophrenia [Whitford et al., 2011]. A subsequent study conducted in adolescent onset schizophrenia demonstrated that while this population is characterized by widely distributed FA decrease [Douaud et al., 2007], dispersion is abnormal specifically in the corpus callosum [Savadjiev et al., 2014a]. Despite wide spread differences in the age of participants between this earlier study by Savad-

jiev et al. [2014a] and the present one (our high-risk population is older than the adolescent sample by 9 years on average), medication dosage (none of our subjects are on antipsychotic medication), FA changes (adolescent schizophrenics were characterized by widely distributed changes in FA, while our high-risk subjects showed no FA changes), dispersion changes are strikingly similar across these two studies. While absolute dispersion values may change with age, as well as with diagnosis, the pattern of change, and its gender specificity, are preserved. Future studies may also link white matter dispersion changes to gene expression, as has been done with recent cortical surface genetic mapping [Chen et al., 2012].

So far, only a relatively small number of diffusion MRI studies of the white matter in familial high risk for schizophrenia have been conducted. Most of them focus on the FA measure, and report fairly disparate findings. For instance, some studies report decreased FA [within anterior limb of the internal capsule—Munoz Maniega et al., 2008; corpus callosum and cingulum bundle—Camchong et al., 2009; frontal WM—Hoptman et al., 2008], or increased FA in subjects at high familial risk, compared to controls [frontal WM—Hoptman et al., 2008]. Other studies have investigated subjects at clinical increased risk to develop schizophrenia (ultra high risk, or prodromal), with similar discrepancies in their findings: widespread FA reductions [Carletti et al., 2012], no differences between ultra high-risk and control subjects [Peters et al., 2008], and FA increases [WM—Bloemen et al., 2010; AF—Boos et al., 2013].

As exposed above in the Introduction section of this article, FA is a nonspecific measure that reflects tissue “integrity.” In the present article, we argue that measures of macrostructural white matter geometry present a more robust alternative to FA, and would be reflective of biological processes rooted specifically in neurodevelopment. In light of this, it is striking that our geometry measures would reveal a very similar pattern of sexual dimorphism reversal in both familial high risk for schizophrenia, as well as in adolescent onset schizophrenia [Savadjiev et al., 2014a]. One of the strengths of the SHD measure of dispersion [Savadjiev et al., 2010] used here is that computes white matter geometry independently from any tractography method. Because tractography can be unreliable, the SHD method computes white matter geometry directly from the diffusion tensor field, completely bypassing the need for tractography. While it does compute a white matter dispersion value at each voxel, it does so based on geometrical information within a larger neighborhood of voxels, that is, it describes the geometry of the white matter over several millimeters or centimeters. Thus, it reflects *macrostructural* geometry. This is in contrast to the NODDI method [Zhang et al., 2012], which has gained popularity over the recent years, and which computes a model of neurite orientation dispersion within individual voxels, and is thus related more to the sub-millimeter microstructure of the white matter. Thus, the information carried by the SHD and NODDI measures is very different.

To perform an analysis of the SHD measure, in this study we took advantage of the processing framework provided by TBSS [Smith et al., 2006]. This framework extracts the relevant SHD features from each subject and projects them onto a structure common across the subjects, the TBSS skeleton. This TBSS procedure of “data skeletonization” is widely used in the literature, and it makes comparisons across subjects particularly easy. Furthermore, it is completely independent of tractography. Of course, like any other analysis procedure, TBSS has its own limitations, as discussed for instance in Schwarz et al. [2014], and Edden and Jones [2011]. Several methods for tract-based comparison exist as alternatives to TBSS. However, despite the known limitations of TBSS, we chose to use it in the present work for two main reasons. The first is to facilitate a comparison between the present results in a familial high risk cohort, and our previously reported results in adolescent-onset schizophrenia [Savadjiev et al., 2014a]. Furthermore, as discussed earlier, our SHD measure is not tied to tractography. To preserve this independence from tractography throughout the entire analysis pipeline, we chose to work with a voxel-based method like TBSS as opposed to other possible tractography-based alternatives.

In summary, our results show that neuroimaging measures of macrostructural white matter geometry may reveal early developmental abnormalities common to both diagnosed schizophrenic patients and to high-risk subjects. This is an important step toward the goal of defining image-based markers of schizophrenia risk that can capture developmental deviations prior to symptom onset. Our results are significant at the 0.05 level, but not at the 0.01 level. This is a limitation of our study, together with the relatively small population sample that we work with. Nevertheless, this is the first study to look at a white matter abnormality of geometric nature in a familial high-risk population, and our results replicate findings recently published by us in early onset schizophrenia population [Savadjiev et al., 2014a]. Thus, we believe the present article supports the view that this direction of research is promising, and that more work needs to be done on novel structural image markers specific to the white matter, as they may reflect important neurodevelopmental processes not captured by standard neuroimaging measures.

ACKNOWLEDGMENT

The authors thank Martha Shenton, Lynn DeLisi, and Amanda Lyall for valuable scientific discussions, and Paula Pelavin for help in data processing.

REFERENCES

Annett M (1985): Left, Right, Hand and Brain: The Right-Shift Theory. London: Erlbaum.
 Armstrong E, Schleicher A, Omran H, Curtis M, Zilles K (1995): The ontogeny of human gyrification. *Cereb Cortex* 5:56–63.

Basser PJ (1997): New histological and physiological stains derived from diffusion-tensor MR images. *Ann NY Acad Sci* 820:123–138.
 Bloemen OJ, de Koning MB, Schmitz N, Nieman DH, Becker HE, de Haan L, Dingemans P, Linszen DH, van Amelsvoort TA (2010): White-matter markers for psychosis in a prospective ultra-high-risk cohort. *Psychol Med* 40: 1297–1304.
 Boos HB, Mandl RC, van Haren NE, Cahn W, van Baal GC, Kahn RS, Hulshoff-Pol HE (2013): Tract-based diffusion tensor imaging in patients with schizophrenia and their non-psychotic siblings. *Eur Neuropsychopharmacol* 23:295–304.
 Camchong J, Lim KO, Sponheim SR, Macdonald AW (2009): Frontal white matter integrity as an endophenotype for schizophrenia: Diffusion tensor imaging in monozygotic twins and patients’ nonpsychotic relatives. *Front Hum Neurosci* 3:35.
 Cannon-Spoor HE, Potkin SG, Wyatt RJ (1982): Measurement of premorbid adjustment in chronic schizophrenia. *Schizophr Bull* 8:470–484.
 Carletti F, Woolley JB, Bhattacharyya S, Perez-Iglesias R, Fusar-Poli P, Valmaggia L, Broome MR, Bramon E, Johns L, Giampietro V, Williams SC, Barker GJ, McGuire PK (2012): Alterations in white matter evident before the onset of psychosis. *Schizophr Bull* 38:1170–1179.
 Catani M, Mesulam M (2008): The arcuate fasciculus and the disconnection theme in language and aphasia: History and current state. *Cortex* 44:953–961.
 Chen CH, Gutierrez ED, Thompson W, Panizzon MS, Jernigan TL, Eyler LT, Fennema-Notestine C, Jak AJ, Neale MC, Franz CE, Lyons MJ, Grant MD, Fischl B, Seidman LJ, Tsuang MT, Kremen WS, Dale AM (2012): Hierarchical genetic organization of human cortical surface area. *Science* 335:1634–1636.
 Crow TJ, Paez P, Chance SE (2007): Callosal misconnectivity and the sex difference in psychosis. *Int Rev Psychiatry* 19:449–457.
 Dehay C, Giroud P, Berland M, Killackey H, Kennedy H (1996): Contribution of thalamic input to the specification of cytoarchitectonic cortical fields in the primate: Effects of bilateral enucleation in the fetal monkey on the boundaries, dimensions, and gyrification of striate and extrastriate cortex. *J Comp Neurol* 367:70–89.
 Douaud G, Smith S, Jenkinson M, Behrens T, Johansen-Berg H, Vickers J, James S, Voets N, Watkins K, Matthews PM, James A (2007): Anatomically related grey and white matter abnormalities in adolescent-onset schizophrenia. *Brain* 130:2375–2386.
 Edden RA, Jones DK (2011): Spatial and orientational heterogeneity in the statistical sensitivity of skeleton-based analyses of diffusion tensor MR imaging data. *J Neurosci Methods* 201: 213–219.
 Fitts-Jones J, Kubicki M, Shenton ME (2013): Review of functional and anatomical brain connectivity findings in schizophrenia. *Curr Opin Psychiatry* 26:172–187.
 Goldman-Rakic PS (1980): Morphological consequences of prenatal injury to the primate brain. *Prog Brain Res* 53:3–19.
 Goldman-Rakic PS, Rakic P (1984): Experimental modification of gyral patterns. In: Geschwind N, Galaburda AM, editors. *Cerebral Dominance: The Biological Foundation*. Cambridge, MA: Harvard University Press, pp 179–192.
 Goldstein JM, Seidman LJ, Makris N, Ahern T, O’Brien LM, Caviness VSJ, Kennedy DN, Faraone SV, Tsuang MT (2007): Hypothalamic abnormalities in schizophrenia: Sex effects and genetic vulnerability. *Biol Psychiatry* 61:935–945.
 Harris JM, Moorhead TW, Miller P, McIntosh AM, Bonnici HM, Owens DG, Johnstone EC, Lawrie SM (2007): Increased

- prefrontal gyrification in a large high-risk cohort characterizes those who develop schizophrenia and reflects abnormal prefrontal development. *Biol Psychiatry* 62:722–729.
- Hoptman MJ, Nierenberg J, Bertisch HC, Catalano D, Ardekani BA, Branch CA, Delisi LE (2008): A DTI study of white matter microstructure in individuals at high genetic risk for schizophrenia. *Schizophr Res* 106:115–124.
- Jones DK, Knösche TR, Turner R (2013): White matter integrity, fiber count, and other fallacies: The do's and don'ts of diffusion MRI. *Neuroimage* 73:239–254.
- Kubicki M, McCarley RW, Westin C-F, Park HJ, Maier S, Kikinis R, Jolesz FA, Shenton ME (2007): A review of diffusion tensor imaging studies in schizophrenia. *J Psychiatr Res* 41:15–30.
- Lewis DA (2011): Antipsychotic medications and brain volume: Do we have cause for concern? *Arch Gen Psychiatry* 68:126–127.
- Lewis DA, Levitt P (2002): Schizophrenia as a disorder of neurodevelopment. *Annu Rev Neurosci* 25:409–432.
- Munoz Maniega S, Lymer GK, Bastin ME, Marjoram D, Job DE, Moorhead TW, Owens DG, Johnstone EC, McIntosh AM, Lawrie SM (2008): A diffusion tensor MRI study of white matter integrity in subjects at high genetic risk of schizophrenia. *Schizophr Res* 106:132–139.
- Nichols TE, Holmes AP (2002): Nonparametric permutation tests for functional neuroimaging: A primer with examples. *Hum Brain Mapp* 15:1–25.
- Pantelis C, Yücel M, Wood SJ, McGorry PD, Velakoulis D (2003): Early and late neurodevelopmental disturbances in schizophrenia and their functional consequences. *Aust N Z J Psychiatry* 37:399–406.
- Peters BD, de Haan L, Dekker N, Blaas J, Becker HE, Dingemans PM, Akkerman EM, Majoie CB, van Amelsvoort T, den Heeten GJ, Linszen DH (2008): White matter fibertracking in first-episode schizophrenia, schizoaffective patients and subjects at ultra-high risk of psychosis. *Neuropsychobiology* 58:19–28.
- Peters BD, Blaas J, de Haan L (2010): Diffusion tensor imaging in the early phase of schizophrenia: What have we learned? *J Psychiatr Res* 44:993–1004.
- Rajagopalan V, Scott J, Habas PA, Kim K, Corbett-Detig J, Rousseau F, et al. (2011): Local tissue growth patterns underlying normal fetal human brain gyrification quantified *in utero*. *J Neurosci* 31:2878–2887.
- Savadjiev P, Kindlmann GL, Bouix S, Shenton ME, Westin CF (2010): Local white geometry from diffusion tensor gradients. *Neuroimage* 49:3175–3186.
- Savadjiev P, Whitford TJ, Hough ME, Clemm von Hohenberg C, Bouix S, Westin CF, Shenton ME, Crow TJ, James AC, Kubicki M (2014a): Sexually dimorphic white matter geometry abnormalities in adolescent onset schizophrenia. *Cereb Cortex* 24:1389–1396.
- Savadjiev P, Rathi Y, Bouix S, Smith AR, Schultz RT, Verma R, Westin CF (2014b): Fusion of white and gray matter geometry: A framework for investigating brain development. *Med Image Anal* 18:1349–1360.
- Schwarz CG, Reid RI, Gunter JL, Senjem ML, Przybelski SA, Zuk SM, Whitwell JL, Vemuri P, Josephs KA, Kantarci K, Thompson PM, Petersen RC, Jack CR, Alzheimer's Disease Neuroimaging Initiative (2014): Improved DTI registration allows voxel-based analysis that outperforms tract-based spatial statistics. *Neuroimage* 94:65–78.
- Smith SM, Nichols TE (2009): Threshold-free cluster enhancement: Addressing problems of smoothing, threshold dependence and localisation in cluster inference. *Neuroimage* 44:83–98.
- Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, Watkins KE, Ciccarelli O, Cader MZ, Matthews PM, Behrens TEJ (2006): Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data. *Neuroimage* 31:1487–1505.
- Taylor DC (2003): Schizophrenias and epilepsies: Why? When? How? *Epilepsy Behav* 4:474–482.
- Thermenos HW, Keshavan MS, Juelich RJ, Molokotos E, Whitfield-Gabrieli S, Brent BK, Makris N, Seidman LJ (2013): A review of neuroimaging studies of young relatives of individuals with schizophrenia: A developmental perspective from schizotaxia to schizophrenia. *Am J Med Genet B Neuropsychiatr Genet* 162B:604–635.
- Tristán-Vega A, Aja-Fernández S, Westin C-F (2012): Least squares for diffusion tensor estimation revisited: Propagation of uncertainty with Rician and non-Rician signals. *Neuroimage* 59:4032–4043.
- Uehara-Aoyama K, Nakamura M, Asami T, Yoshida T, Hayano F, Roppongi T, Fujiwara A, Inoue T, Shenton ME, Hirayasu Y (2011): Sexually dimorphic distribution of orbitofrontal sulcogyral pattern in schizophrenia. *Psychiatry Clin Neurosci* 65:483–489.
- Whitford TJ, Savadjiev P, Kubicki M, O'Donnell LJ, Terry DP, Bouix S, Westin C-F, Schneiderman JS, Bobrow L, Rausch AC, Niznikiewicz M, Nestor PG, Pantelis C, Wood SJ, McCarley RW, Shenton ME (2011): Fiber geometry in the corpus callosum in schizophrenia: Evidence for transcallosal misconnection. *Schizophrenia Res* 132:69–74.
- Zhang H, Schneider T, Wheeler-Kingshott CA, Alexander DC (2012): NODDI: Practical in vivo neurite orientation dispersion and density imaging of the human brain. *Neuroimage* 61:1000–1016.