Published in final edited form as:

Psychiatry Res. 2009 November 30; 174(2): 110–115. doi:10.1016/j.psychres.2009.04.014.

White matter ‘potholes’ in early-onset schizophrenia: a new approach to evaluate white matter microstructure using diffusion tensor imaging

Tonya White^{*,a,b,c}, Marcus Schmidt^a, and Canan Karatekin^{c,d}

^a Division of Child and Adolescent Psychiatry, University of Minnesota, Minneapolis, MN

^b Center for Magnetic Resonance Research, University of Minnesota, Minneapolis, MN

^c Center for Neurobehavioral Development, University of Minnesota, Minneapolis, MN

^d Institute of Child Development, University of Minnesota, Minneapolis, MN

Abstract

There is considerable evidence implicating white matter abnormalities in the pathophysiology of schizophrenia. Many of the recent studies examining white matter have utilized diffusion tensor imaging (DTI) using either region of interest (ROI) or voxel based approaches. Both voxel-based and ROI approaches are based on the assumption that the abnormalities in white matter overlap spatially. However, this is an assumption that has not been tested and it is possible that aberrations in white matter occur in non-overlapping regions. In order to test for the presence of non-overlapping regions of aberrant white matter, we developed a novel image processing technique that evaluates for white matter ‘potholes,’ referring to within-subject clusters of white matter voxels that show a significant reduction in fractional anisotropy. We applied this algorithm to a group of children and adolescents with schizophrenia compared to controls and found an increased number of ‘potholes’ in the patient group. These results suggest that voxel-based and ROI approaches may be missing some white matter differences that do not overlap spatially. This algorithm may be also be well suited to detect white matter abnormalities in disorders such as substance abuse, head trauma, or specific neurological conditions affecting white matter.

Keywords

DTI; Imaging Methods; Early-Onset Schizophrenia; Potholes

1. Introduction

White matter (WM) tracts within the brain consist of myelinated neuronal fibers that serve as ‘superhighways’ for the rapid transfer of information between brain regions. Medical disorders that disrupt these pathways, such as multiple sclerosis or amyotrophic lateral sclerosis can profoundly affect various aspects of cognitive and motor function (Gilmore et al., 2008).

Corresponding Author: Tonya White, M.D., Assistant Professor, Division of Child and Adolescent Psychiatry F256/2B, University of Minnesota, Fairview University Medical Center, 2450 Riverside Ave., Minneapolis, MN 55454, tel. 612.273.9762, fax. 612.273.9779, twhite@umn.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Schizophrenia is a severe mental illness that involves a constellation of clinical symptoms and global cognitive deficits. While the etiology of schizophrenia is yet unknown, one current hypothesis is a disruption in brain connectivity (Friston and Frith, 1995). Thus, cerebral WM has become a source of considerable investigation in schizophrenia, with recent evidence supporting WM abnormalities based on postmortem samples (Davis et al., 2003; Heckers et al., 1991; Karoutzou et al., 2008; Uranova et al., 2007), genetic analyses (Hakak et al., 2001), and diffusion tensor imaging (DTI) (Kanaan et al., 2005; Kubicki et al., 2007; Kyriakopoulos et al., 2008; White et al., 2008).

There are now close to 60 studies that have utilized DTI to assess WM microstructure in schizophrenia (White et al., 2008). What is most striking about the combined findings of these studies is the considerable heterogeneity in the locations of the WM differences between patients and controls (Kanaan et al., 2005; Kubicki et al., 2007; White et al., 2008). While there does appear to be an over-representation of abnormalities in the corpus callosum, cingulate bundle, and frontal WM, nearly every WM structure has been implicated. Since the majority of DTI studies utilize voxel-based techniques to evaluate regional WM differences, typically only positive findings are reported. However, the whole brain testing inherent in voxel-based approaches is also associated with widespread areas that do not demonstrate significant patient/control differences. These negative results complicate the interpretation of DTI findings in patients with schizophrenia.

While a few early studies have reported a diffuse pattern of WM abnormalities in patients with schizophrenia (Agartz et al., 2001; Flynn et al., 2003), most DTI studies tend to have focal abnormalities (White et al., 2008). Perhaps one explanation for the variability in the existing studies involves the methodologies applied to determine the underlying deficits. The current methodologies applied to DTI studies involve either region of interest (ROI) or voxel-based techniques. Both ROI and voxel-based approaches make an assumption that WM abnormalities are spatially localized to specific regions in patients. For example, for ROI or voxel-based approaches to detect an abnormality of the cingulate bundle, the WM deficit would need to be spatially localized to the same region of the cingulate bundle in most of the patients. However, a deficit could occur at different locations along the cingulate tract and have a similar contribution to the clinical deficit. While spatial smoothing can be applied to account for this variability (Jones et al., 2005), it is limited to regions that are proximally located (White et al., 2001). There have been recent studies using tractography approaches that support this weakness of ROI approaches (Kanaan et al., 2006).

It is possible that disruptions in WM integrity may occur at different 'points of weakness' in different individuals. Disorders such as tuberous sclerosis (Inoue et al., 1988; Makki et al., 2007) and multiple sclerosis (Gilmore et al., 2008) may have heterogeneity in affected WM pathways, and there may be similar heterogeneous patterns in the location of WM abnormalities in schizophrenia. While primary WM disorders may not be directly compared to schizophrenia, we only note the assumption of spatially overlapping regions has not been confirmed. In fact, the heterogeneity of the results in the current studies may be a result of the analytic strategies and voxel based or ROI approaches, that are powerful for evaluating gray matter differences, may not be as well suited to identify specific WM abnormalities.

The goal of this study was to evaluate a novel approach to examine WM abnormalities that does not require spatially overlapping deficits. Much in the way that we would not expect potholes to overlap when highways were placed one on top of one another, we developed an algorithm to detect WM 'potholes.' A 'pothole' is a region of WM where a cluster of voxels fall significantly below its voxel-based mean. This algorithm was applied to a dataset of individuals with early onset schizophrenia, defined as those who develop the illness during childhood or adolescence. EOS has been shown to be on a continuum with the adult form of

the illness (Rapoport et al., 1999; Rapoport and Inoff-Germain, 2000), although those with EOS tend to have greater genetic loading (Asarnow et al., 2001) and more pronounced negative symptoms (Frazier et al., 2007; Rabe-Jablonska and Gmitrowicz, 2000) than those with adult-onset schizophrenia.

2. Methods

2.1 Subjects

The participants included 29 patients (18 males and 11 females) with a diagnosis of schizophrenia (n=22), schizoaffective disorder (n=4), or schizophreniform disorder (n=3). The control group consisted of 41 healthy volunteers (25 males and 16 females). Each participant, including the healthy volunteers, underwent a diagnostic evaluation using the Kiddie-SADS-PL (Kaufman et al., 1997). Additional clinical measures included the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983), Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984), and the Anchored Brief Psychiatric Rating Scale for Children (BPRS-C) (Lachar et al., 2001). The mean age of the patient group was 14.8 (S.D. 2.8) years, and the mean age of the healthy volunteers was 14.2 (S.D. 3.4) years (age range 8 to 19).

The control group had no evidence of a past or present psychiatric disorder and no history of schizophrenia or psychosis in a first degree relative. Patients and controls were excluded if they had a history of substance dependence, ongoing substance abuse (within the past month), IQ less than 70, or a neurological disorder, head injury, or medical illness involving the brain. The study was approved by the Institutional Review Board at the University of Minnesota and informed consent and assent were obtained prior to participation.

2.2 MRI Sequence

All MR images were acquired with a 3T Siemens MR System (Erlangen, Germany) at the Center for Magnetic resonance Research in University of Minnesota. After a localizer sequence for orientation, a high resolution, three-dimensional FLASH 3-D volumetric acquisition (TR = 18 msec TR = 4.73 sec, flip angle=25, FOV = 240 mm isotropic, in-plane resolution of 0.625 × 0.625 mm and a slice thickness of 1.5 mm, average=1) was collected for each subject. From these images, anterior commissure (AC) and posterior commissure (PC) planes were identified.

Diffusion Tensor Imaging was performed with a full tensor diffusion MRI sequence based on a single shot spin echo planar technique (TR=11 sec TE=104 msec, FOV=256 mm isotropic, in-plane resolution of 2 × 2 mm and a slice thickness of 2 mm, averages=3). The images were acquired in twelve non-collinear directions (b=1000 s/mm²) and one image with no diffusion encoding (b=0s/mm²). Diffusion weighted images were acquired along the AC-PC plane.

2.3 Image Processing

Pre-processing of the images were performed using Freesurfer (Dale et al., 1999), FSL (Smith et al., 2004), and FSL's Tract Based Spatial Statistics (TBSS) (Smith et al., 2006). Raw diffusion weighted images were converted from DICOM to nifti using Freesurfer (Dale et al., 1999). Individual images were eddy current corrected, motion corrected, and fractional anisotropy (FA) images were created by fitting a tensor model to the diffusion data using FMRIB's Diffusion Toolbox (FDT) (Smith et al., 2004). The brain was extracted using BET (Smith, 2002). All subjects' FA data were then aligned into a common space using the nonlinear registration tool FNIRT (Andersson et al., 2007a, 2007b), which uses a b-spline representation of the registration warp field (Rueckert et al., 1999). Next, the mean FA image was created and thinned to create a mean FA skeleton which represents the midpoint of all tracts common

to the group. Each subject's aligned FA data was then projected onto this skeleton and the resulting data fed into voxelwise cross-subject statistics.

In addition to the group comparison using TBSS, we utilized an in-house program in Matlab in order to quantify the number of WM 'potholes' along the major WM tracts (Figure 1). This process started with FA images that have undergone non-linear registration into MNI space using TBSS. These images did not undergo spatial filtering. The first step generated a voxel-by-voxel mean and standard deviation images of the control subjects. These group and SD images were then used to individually create a voxel-wide z-image for every subject, with each voxel based on the mean and standard deviation of the control group. To ensure the search involved only WM regions, each image was masked with the cortical areas defined by the Johns Hopkins University WM atlas (Mori et al., 2008;Wakana et al., 2004). In addition, only regions in which all subjects had an FA > 0.2 were utilized. This resulted in 71 WM masked z-transformed FA images, one for each subject. The individual z-FA images were used to search for clusters of WM that fell below a set z-threshold and were greater than a specified cluster size. Clusters were determined by thresholding each image and labeling the 3-dimensional connectivities (26 neighboring voxels). To evaluate the spatial location of the individual WM potholes, the volume of each pothole was evaluated for each label of the WM atlas.

2.4 Statistical Analyses

Demographic and IQ information was evaluated using chi square for bivariate data and t-tests for continuous data. To provide a comprehensive assessment of this method, we systematically varied the minimum z-threshold and cluster volume. We started at voxels at least one standard deviation below the mean and decremented the threshold by 0.1 to five standard deviations below the mean. For each iteration of the new threshold, we incremented the cluster size from values that exceeded 1 voxel to those that exceeded 1,000 voxels. Statistical analyses on the imaging data were performed using Matlab (The Mathworks, Natick, MA). To evaluate anatomical regions of interest (ROI) and reduce the number of tests, we performed a 2 (diagnosis) by 48 (region) mixed-model repeated measure ANOVA. Post-hoc tests were performed on individual regions using Wilcoxon rank-order tests. Spearman Correlation Coefficients were utilized to evaluate the relationship between the demographic and clinical measures and the FA potholes. Statistical analyses were performed utilizing the SAS statistical package (Cary, NC, USA).

3. Results

There were no significant differences between age, sex, and handedness between EOS patients and controls (See Table 1). However, there was a significant difference in SES between patients and controls ($t = 4.4$, $df = 45.2$, $p < 0.01$). There were no statically significant differences in the number of potholes between males and females, however, there was an age effect with potholes smaller than 0.3 cc in volume. Younger subjects had an inverse correlation between age and the number of potholes (Spearman $r = -0.32$, $p < 0.01$). There were no significant correlations between the number of potholes and age once the minimum number of voxels in the cluster exceeded a volume of 0.3 cc.

Patients with EOS had a greater number of voxel clusters that dipped significantly below the voxel-based group mean. At thresholds of less than 2 standard deviations below the mean, the median number of clusters with at least 50 contiguous voxels was 27.5 in patients and 20 in controls, with a maximum of 59 in patients and 35 in controls. Increasing the number of contiguous voxels to at least 200 resulted in a median of 6 potholes in patients, and 3 in controls, with a maximum number of 23 and 13 in patients and controls, respectively. At none of the thresholds or minimum voxel clusters did controls have a significantly greater number of potholes than patients (Figure 2). Patients had a significantly greater number of potholes

compared to controls at 57 different thresholds (Wilcoxon Rank-Order test $p < 0.05$). The p values for different thresholds and minimum cluster sizes can be seen in Figure 1-f.

Anatomically Defined Region of Interest Analyses

The specific ROIs were defined using the Johns Hopkins University Human Brain White Matter Atlas (Mori et al., 2008; Oishi et al., 2008). A 2 (diagnosis) by 48 (region) repeated measures mixed model ANOVA found highly significant effects of diagnosis for the volume of potholes within each region ($F_{1,69} = 10.9$, $p < 0.003$) and the mean FA within potholes ($F_{1,69} = 19.3$, $p < 0.0001$). The individual differences between patients and controls that were less than $p < 0.01$ are shown in Table 2. Figure 3-a demonstrates locations of potholes in patients compared to controls. A Spearman rank order correlation was used to evaluate the relationship between the number of potholes and the duration of illness in those regions that were different between patients and controls. There was a significantly positive correlation between the duration of illness and the number of potholes in the right inferior fronto-occipital fasciculus ($r = 0.42$, $p = 0.03$).

Comparison with TBSS Analyses

The voxelwise group analysis using TBSS and the most conservative permutation-based nonparametric algorithm (Smith et al., 2006) corrected for multiple comparisons at the $p < 0.05$ level found no differences between patients and controls. When relaxing the criteria to a corrected threshold of $p < 0.10$, patients had lower FA in several regions that were also identified using the pothole approach. These regions included the corpus callosum and frontal WM regions (Figure 3-b). Using this same relaxed threshold, there were no regions in which controls had lower FA than patients.

4. Discussion

Voxel-based and ROI techniques are powerful methods to detect group differences in brain structure and function. However, the underlying assumption of both of these techniques is that the group differences are localized to the same brain region in at least the majority of patients. It is yet unknown if WM pathology occurs in the same location in each patient with schizophrenia. In fact, the currently DTI literature has considerable variability in the location of WM findings (Kanaan et al., 2005; White et al., 2008). If there are individual differences in the location of the WM abnormalities, both ROI and voxel based approaches may lack the power to identify these differences. In addition, it is possible that variability in the location of WM abnormalities may contribute to the clinical heterogeneity of schizophrenia.

To test for spatially heterogeneous abnormalities in FA, we developed an algorithm to detect contiguous voxels that fall below their voxel-based mean. This method is able to detect clusters between individuals that differ in brain location, but are localized within the WM. These we labeled WM potholes. We found that patients with EOS demonstrated a significantly greater number of WM potholes compared to matched controls. Since this is a novel approach, we tested the method across a number of different z-scores and volume thresholds (see Figure 1-f). The patient group had significantly greater number of 'potholes' at multiple thresholds and cluster sizes. These clusters are most prominent at approximately 2 standard deviations below the mean and have sizes that exceed 1,000 voxels (1 cc), which were found in the corpus callosum. The control group did not have a significantly greater number of 'potholes' than patients at any threshold or volume.

Interestingly, the spatial location of these potholes did emerge in regions that have been identified commonly in studies of schizophrenia. For example, numerous studies have identified aberrant WM regions in the corpus callosum, cingulate bundle, and frontal WM tracts

(Kyriakopoulos et al., 2008; White et al., 2008). Utilizing the standard TBSS approach, we did not find any regions which were different between patients and controls. However, with a less conservative threshold for multiple testing, we found significant differences in the corpus callosum and frontal WM regions, regions which overlap with the pothole approach. Thus, it is possible that certain regions that have a convergence of WM pathways, such as the corpus callosum, are more likely have an overlap of WM abnormalities, which are then detected using voxel-based techniques.

Considering the variability of WM pathology in disorders such as multiple sclerosis (Gilmore et al., 2008), it is possible that similar heterogeneous patterns may also exist in the WM pathology found in schizophrenia. While there may be involvement in multiple regions of the brain, certain areas, such as the cingulate bundle, corpus callosum, or frontal WM tracts, may be more susceptible to alterations. This would account for the overrepresentation of positive findings in these regions using voxel based and ROI studies. However, other individuals or subgroups may have different areas of susceptibility that are based on genetic or environmental influences. One possible etiology would involve disruptions in the distribution or number of oligodendrocytes. Postmortem studies of schizophrenia often focus on specific regions and thus do not provide a gross distribution of abnormalities. However, postmortem studies have identified abnormal numbers of oligodendrocytes in the prefrontal cortex (Uranova et al., 2004; Uranova et al., 2007) and cingulum (Stark et al., 2004).

While it was not a goal of this paper to assess developmental differences in the number of potholes, we did find an inverse correlation between potholes and age; i.e., younger children tended to have a greater number of smaller potholes. Since studies using both postmortem and DTI methods have demonstrated an increase in FA that is associated with development, this technique may be beneficial to identify regions associated with neurodevelopmental processes such as myelination. Future work using this technique with larger populations of typically developing children will be necessary to confirm this finding. Finally, we found a significant positive correlation between the duration of illness and the right inferior fronto-occipital fasciculus. Since these EOS patients are in the early stages of their illness (mean duration of illness was 2.3 years), a greater range of illness duration or a longitudinal design would be best suited to evaluate the relationship between illness duration and the number of potholes. This is important since there is evidence that patients with chronic schizophrenia have regions of lower FA has compared to first-episode patients (Friedman et al., 2008).

This is a preliminary investigation of a novel method to assess WM microstructure in clinical populations and we note that there are several limitations to the study. We have a relatively small sample size, although the detection of differences in a small sample actually reflects large effect sizes. It would be beneficial to apply the method to a larger dataset with both a first-episode and chronic patient groups, since a progression of WM abnormalities has been demonstrated between first-episode and chronic groups (Friedman et al., 2008). Finally, we used the Johns Hopkins WM atlas to mask the region in which we searched for contiguous voxels falling below a set threshold. While we attempted to control for multiple tests, some of the potholes may be false positives. However, it would be expected that there would be an equal number of false positives present in both the EOS and control groups. Yet, we demonstrated a greater number of potholes in the patient group across different thresholds and cluster sizes. At any threshold or minimum cluster size, the control group never had a greater number of potholes compared to the patient group.

In summary, we describe a novel approach to detect WM abnormalities that may not be detected using ROI or voxel-based approaches. This algorithm was applied to a group of patients with EOS and the patient group had a significantly greater number of WM potholes compared to the control group. Variations of this algorithm could be used to assess for local minima within

z-transformed FA maps rather than our approach of thresholding the WM maps. In addition, reductions of the variance may be obtained by regressing variables such as age into the model that have been shown to have an effect on FA.

Acknowledgments

This work was funded through NIMH K08 MH068540 and by the National Alliance for Research in Schizophrenia and Affective Disorders (NARSAD) through an Essel Foundation grant. We would like to acknowledge the anonymous reviewers for their helpful suggestions. We also acknowledge MRI infrastructure grants: P30 NS057091 & P41 RR008079

References

- Agartz I, Andersson JL, Skare S. Abnormal brain white matter in schizophrenia: a diffusion tensor imaging study. *Neuroreport* 2001;12(10):2251–2254. [PubMed: 11447344]
- Andersson, J.; Jenkinson, M.; Smith, S. Non-linear optimisation. FMRIB technical report TR07JA1. 2007a. from www.fmrib.ox.ac.uk/analysis/techrep
- Andersson, J.; Jenkinson, M.; Smith, S. Non-linear registration, aka Spatial normalisation. FMRIB technical report TR07JA2. 2007b. from www.fmrib.ox.ac.uk/analysis/techrep
- Andreasen, NC. The Scale for the Assessment of Negative Symptoms (SANS), Vol. The University of Iowa; 1983.
- Andreasen, NC. The Scale for the Assessment of Positive Symptoms (SAPS), Vol. The University of Iowa; 1984.
- Asarnow RF, Nuechterlein KH, Fogelson D, Subotnik KL, Payne DA, Russell AT, Asamen J, Kuppinger H, Kendler KS. Schizophrenia and schizophrenia-spectrum personality disorders in the first-degree relatives of children with schizophrenia: the UCLA family study. *Arch Gen Psychiatry* 2001;58(6): 581–588. [PubMed: 11386988]
- Dale AM, Fischl B, Sereno MI. Cortical surface-based analysis. I. Segmentation and surface reconstruction. *Neuroimage* 1999;9(2):179–194. [PubMed: 9931268]
- Davis KL, Stewart DG, Friedman JI, Buchsbaum M, Harvey PD, Hof PR, Buxbaum J, Haroutunian V. White matter changes in schizophrenia: evidence for myelin-related dysfunction. *Arch Gen Psychiatry* 2003;60(5):443–456. [PubMed: 12742865]
- Flynn SW, Lang DJ, Mackay AL, Goghari V, Vavasour IM, Whittall KP, Smith GN, Arango V, Mann JJ, Dwork AJ, Falkai P, Honer WG. Abnormalities of myelination in schizophrenia detected in vivo with MRI, and postmortem with analysis of oligodendrocyte proteins. *Mol Psychiatry* 2003;8(9):811–820. [PubMed: 12931208]
- Frazier JA, McClellan J, Findling RL, Vitiello B, Anderson R, Zablotsky B, Williams E, McNamara NK, Jackson JA, Ritz L, Hlastala SA, Pierson L, Varley JA, Puglia M, Maloney AE, Ambler D, Hunt-Harrison T, Hamer RM, Noyes N, Lieberman JA, Sikich L. Treatment of early-onset schizophrenia spectrum disorders (TEOSS): demographic and clinical characteristics. *J Am Acad Child Adolesc Psychiatry* 2007;46(8):979–988. [PubMed: 17667477]
- Friedman JI, Tang C, Carpenter D, Buchsbaum M, Schmeidler J, Flanagan L, Golembo S, Kanellopoulou I, Ng J, Hof PR, Harvey PD, Tsopelas ND, Stewart D, Davis KL. Diffusion tensor imaging findings in first-episode and chronic schizophrenia patients. *Am J Psychiatry* 2008;165(8):1024–1032. [PubMed: 18558643]
- Friston KJ, Frith CD. Schizophrenia: a disconnection syndrome? *Clin Neurosci* 1995;3(2):89–97. [PubMed: 7583624]
- Gilmore CP, Donaldson I, Bo L, Owens T, Lowe JS, Evangelou N. Regional variations in the extent and pattern of grey matter demyelination in Multiple Sclerosis: a comparison between the cerebral cortex, cerebellar cortex, deep grey matter nuclei and the spinal cord. *J Neurol Neurosurg Psychiatry*. 2008
- Hakak Y, Walker JR, Li C, Wong WH, Davis KL, Buxbaum JD, Haroutunian V, Fienberg AA. Genome-wide expression analysis reveals dysregulation of myelination-related genes in chronic schizophrenia. *Proc Natl Acad Sci U S A* 2001;98(8):4746–4751. [PubMed: 11296301]
- Heckers S, Heinsen H, Geiger B, Beckmann H. Hippocampal neuron number in schizophrenia. A stereological study. *Arch Gen Psychiatry* 1991;48(11):1002–1008. [PubMed: 1747014]

- Inoue Y, Nakajima S, Fukuda T, Nemoto Y, Shakudo M, Murata R, Matsuoka O, Takemoto K, Matsumura Y, Onoyama Y. Magnetic resonance images of tuberous sclerosis. Further observations and clinical correlations. *Neuroradiology* 1988;30(5):379–384. [PubMed: 3211312]
- Jones DK, Symms MR, Cercignani M, Howard RJ. The effect of filter size on VBM analyses of DT-MRI data. *Neuroimage* 2005;26(2):546–554. [PubMed: 15907311]
- Kanaan RA, Kim JS, Kaufmann WE, Pearlson GD, Barker GJ, McGuire PK. Diffusion tensor imaging in schizophrenia. *Biol Psychiatry* 2005;58(12):921–929. [PubMed: 16043134]
- Kanaan RA, Shergill SS, Barker GJ, Catani M, Ng VW, Howard R, McGuire PK, Jones DK. Tract-specific anisotropy measurements in diffusion tensor imaging. *Psychiatry Res* 2006;146(1):73–82. [PubMed: 16376059]
- Karoutzou G, Emrich HM, Dietrich DE. The myelin-pathogenesis puzzle in schizophrenia: a literature review. *Mol Psychiatry* 2008;13(3):245–260. [PubMed: 17925796]
- Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, Williamson D, Ryan N. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry* 1997;36(7):980–988. [PubMed: 9204677]
- Kubicki M, McCarley R, Westin CF, Park HJ, Maier S, Kikinis R, Jolesz FA, Shenton ME. A review of diffusion tensor imaging studies in schizophrenia. *J Psychiatr Res* 2007;41(12):15–30. [PubMed: 16023676]
- Kyriakopoulos M, Bargiotas T, Barker GJ, Frangou S. Diffusion tensor imaging in schizophrenia. *Eur Psychiatry* 2008;23(4):255–273. [PubMed: 18524546]
- Lachar D, Randle SL, Harper RA, Scott-Gurnell KC, Lewis KR, Santos CW, Saunders AE, Pearson DA, Loveland KA, Morgan ST. The brief psychiatric rating scale for children (BPRS-C): validity and reliability of an anchored version. *J Am Acad Child Adolesc Psychiatry* 2001;40(3):333–340. [PubMed: 11288775]
- Makki MI, Chugani DC, Janisse J, Chugani HT. Characteristics of abnormal diffusivity in normal-appearing white matter investigated with diffusion tensor MR imaging in tuberous sclerosis complex. *AJNR Am J Neuroradiol* 2007;28(9):1662–1667. [PubMed: 17893226]
- Mori S, Oishi K, Jiang H, Jiang L, Li X, Akhter K, Hua K, Faria AV, Mahmood A, Woods R, Toga AW, Pike GB, Neto PR, Evans A, Zhang J, Huang H, Miller MI, van Zijl P, Mazziotta J. Stereotaxic white matter atlas based on diffusion tensor imaging in an ICBM template. *Neuroimage* 2008;40(2):570–582. [PubMed: 18255316]
- Oishi K, Zilles K, Amunts K, Faria A, Jiang H, Li X, Akhter K, Hua K, Woods R, Toga AW, Pike GB, Rosa-Neto P, Evans A, Zhang J, Huang H, Miller MI, van Zijl PC, Mazziotta J, Mori S. Human brain white matter atlas: identification and assignment of common anatomical structures in superficial white matter. *Neuroimage* 2008;43(3):447–457. [PubMed: 18692144]
- Rabe-Jablonska JK, Gmitrowicz A. Clinical Picture and duration of prodromal period of schizophrenia in adolescents. *Arch Psychiatr Psychother* 2000;2(4):31–38.
- Rapoport JL, Giedd JN, Blumenthal J, Hamburger S, Jeffries N, Fernandez T, Nicolson R, Bedwell J, Lenane M, Zijdenbos A, Paus T, Evans A. Progressive cortical change during adolescence in childhood-onset schizophrenia. A longitudinal magnetic resonance imaging study. *Arch Gen Psychiatry* 1999;56(7):649–654. [PubMed: 10401513]
- Rapoport JL, Inoff-Germain G. Update on childhood-onset schizophrenia. *Curr Psychiatry Rep* 2000;2(5):410–415. [PubMed: 11122989]
- Rueckert D, Sonoda LI, Hayes C, Hill DL, Leach MO, Hawkes DJ. Nonrigid registration using free-form deformations: application to breast MR images. *IEEE Trans Med Imaging* 1999;18(8):712–721. [PubMed: 10534053]
- Smith SM. Fast robust automated brain extraction. *Hum Brain Mapp* 2002;17(3):143–155. [PubMed: 12391568]
- Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, Watkins KE, Ciccarelli O, Cader MZ, Matthews PM, Behrens TE. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *Neuroimage* 2006;31(4):1487–1505. [PubMed: 16624579]
- Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, Bannister PR, De Luca M, Drobnjak I, Flitney DE, Niazy RK, Saunders J, Vickers J, Zhang Y, De Stefano N, Brady

- JM, Matthews PM. Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage* 2004;23:S208–219. [PubMed: 15501092]
- Stark AK, Uylings HB, Sanz-Arigita E, Pakkenberg B. Glial cell loss in the anterior cingulate cortex, a subregion of the prefrontal cortex, in subjects with schizophrenia. *Am J Psychiatry* 2004;161(5):882–888. [PubMed: 15121654]
- Uranova NA, Vostrikov VM, Orlovskaya DD, Rachmanova VI. Oligodendroglial density in the prefrontal cortex in schizophrenia and mood disorders: a study from the Stanley Neuropathology Consortium. *Schizophr Res* 2004;67(23):269–275. [PubMed: 14984887]
- Uranova NA, Vostrikov VM, Vikhrevva OV, Zimina IS, Kolomeets NS, Orlovskaya DD. The role of oligodendrocyte pathology in schizophrenia. *Int J Neuropsychopharmacol* 2007;10(4):537–545. [PubMed: 17313698]
- Wakana S, Jiang H, Nagae-Poetscher LM, van Zijl PC, Mori S. Fiber tract-based atlas of human white matter anatomy. *Radiology* 2004;230(1):77–87. [PubMed: 14645885]
- White T, Nelson M, Lim KO. Diffusion tensor imaging in psychiatric disorders. *Top Magn Reson Imaging* 2008;19(2):97–109. [PubMed: 19363432]
- White T, O'Leary D, Magnotta V, Arndt S, Flaum M, Andreasen NC. Anatomic and functional variability: the effects of filter size in group fMRI data analysis. *Neuroimage* 2001;13(4):577–588. [PubMed: 11305887]

Figure 1.

Processing Steps to Determine White Matter Potholes. (A) All subjects FA maps registered to MNI space using Tract-Based Spatial Statistics; (B) Creation of mean and standard deviation images using all subjects; (C) Individual subjects' FA maps were used to create FA z-maps for each subject; (D) z-FA maps masked to the Johns Hopkins white matter atlas; (E) Identification of Potholes by the Identification of Contiguous Voxels that Fall Below a thresholded z-value; (F) Comparison of Patients versus Controls at Different z-Thresholds and Minimum Cluster Sizes.

Figure 2.
Mean Number of Potholes at Different Minimum Pothole Sizes Between Patients and Controls at a Threshold of $z = -2$.

Figure 3.
The representation of Potholes within the brain in Patients Compared to Controls. The red regions identify potholes in patients and blue regions those in controls.

Table 1
Demographic and Clinical Characteristics of the Early-Onset Patients with Schizophrenia and Control Groups

Demographics	Patients	Controls	p
Age	14.2 (3.4)	14.8 (2.8)	0.47
Gender (Male/Female)	18 / 11	25 / 16	0.93
Handedness (Right / Left / Both)	26 / 2 / 1	35 / 2 / 2	0.94
Socio-economic Status	53.7 (9.8)	40.2 (14.1)	<0.01
Clinical Symptoms			
Positive Symptoms	2.6 (1.2)		
Negative Symptoms	2.8 (1.0)		
Disorganized Symptoms	1.9 (1.0)		
Duration of Illness (years)	2.3 (1.8)		

Table 2

White Matter Regions which show Significant Differences in the Volume of Potholes between Patients and Controls.

Brain Region	Side	Volume Patients	Volume Controls	p
Anterior Corpus Callosum	n/a	158.3	99.6	0.002
Middle Corpus Callosum	n/a	661.0	231.3	0.001
Anterior Thalamic Radiation	Right	94.7	10.0	0.007
Inferior Fronto-Occipital Fasciculus	Right	161.9	28.5	<0.00001
Corticospinal Tract	Left	122.2	65.0	0.006
Corticospinal Tract	Right	329.2	60.4	0.002
Superior Corona Radiata	Left	291.2	82.5	0.005
Posterior Corona Radiata	Right	128.7	40.9	0.003
Fronto-Occipital Fasciculus	Right	81.0	23.9	0.0007
Cingulate Bundle	Left	16.2	23.5	<0.01
Anterior Thalamic Radiation	Left	33.6	5.2	0.005
Superior Longitudinal Fasciculus	Right	132.9	40.7	0.002