Published in final edited form as:

Schizophr Res. 2010 January ; 116(1): 99–100. doi:10.1016/j.schres.2009.09.043.

White matter correlates of clinical function in schizophrenia using diffusion tensor imaging

Tal Herbsman^a and Ziad Nahas^{*,b,c}

^aDepartment of Psychiatry; University of Wisconsin-Madison, USA

^bDepartment of Psychiatry; Medical University of South Carolina, Charleston, SC; USA

^cCenter for Advanced Imaging Research (CAIR); Medical University of South Carolina, Charleston, SC; USA

Keywords

schizophrenia; diffusion tensor imaging; cognitive control; voxel based morphometry; multiple comparison error; false detection rate; tract based spatial statistics

Dear Editors:

There is by now a robust body of evidence from the diffusion tensor imaging (DTI) literature that structural differences likely exist in patients with schizophrenias and may be linked to some of the clinical manifestations of this illness¹. DTI is a magnetic resonance imaging technique that measures localized water diffusivity reflecting the geometric properties and directionality of both axonal membrane and myelin in large white matter tracts of the brain. The most often found DTI abnormalities in the brain of patients with schizophrenia include lower prefrontal and temporal lobe FA, as well as lower FA in the anterior cingulum, arcuate and uncinate fasciculi. Far fewer studies have attempted to correlate FA changes with clinical measures^{2–4}. We report on a tract-based spatial statistics (TBSS)⁵ analysis of white matter fractional anisotropy (FA) differences between unmedicated patients with schizophrenia and controls. As a secondary and exploratory analysis, we also report on WM correlates of clinical measures (PANSS, SANS and Calgary depression scale) in the schizophrenia subgroup.

We enrolled thirteen unmedicated subjects (mean age 37.4 years) and sixteen controls (mean age 41.1 years, no DSM-IV axis I diagnosis). Subjects and controls did not differ significantly in any demographic variables except employment status. Subjects with schizophrenia had not used medications for at least two weeks prior to scanning. Subjects' mean PANSS score was 91 +/- 17, mean SANS 47 +/- 16 and Calgary Depression Scale mean 3.6 +/- 3.4. Each participant had MRI scanning performed using a 3T clinical MRI scanner with a SENSE coil (Intera, Philips Medical Systems; Bothell, WA). DTI acquisition consisted of a single-shot spin echo, echo planar imaging acquisition with a parallel imaging factor of 2 and a partial Fourier factor of 80% with TR = 5 seconds, TE = 100 ms, slice thickness = 3 mm, gap = 0.3 mm, field of

© 2009 Elsevier B.V. All rights reserved.

Address correspondence to: Dr. Ziad Nahas; Institute of Psychiatry – Room 502N, 67 President St.; Charleston, SC 29425 USA. Phone: (843) 792-5710; Fax: (843) 792-5702 ; nahasz@musc.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.

view (FOV) = 256mm, number of slices = 30, matrix = 112×112 (interpolated to 256×256). For each slice, one image was acquired with no additional diffusion weighting and six diffusion weighted images with $b=1000$ s/mm² using the scheme described elsewhere⁶. The diffusion-weighted acquisitions were repeated three times and averaged on the scanner to improve the signal to noise ratio. DTI data was processed using FSL (<http://www.fmrib.ox.ac.uk/fsl/>). The resulting FA maps were processed with the standard TBSS algorithm described in detail elsewhere⁵. Tract localization using this skeleton was achieved using a DTI based white matter atlas⁷. We investigated group differences in FA between patients with schizophrenia and controls employing a voxel-wise non-parametric Brunner Munzel test, using the NPM software package (version released on October 12, 2008; <http://www.sph.sc.edu/comd/rorden/npm/>). Voxel-wise FA differences were corrected for multiple comparisons through false discovery rate⁸ threshold of 1% for our primary outcome measure (FA group difference) and 5% for our secondary outcomes (FA correlation with clinical measures).

Table 1 reports the results of the voxel-wise group comparison and correlations. Although this study suffers from several limitations (modest sample size, post-hoc analysis, lack of medication history) our results replicate previously published findings about FA differences in schizophrenia. In general, we found decreased diffusivity in WM tracks of the prefrontal cortex, the SLF as well as extensive and diffuse cerebellar WM, especially in the vicinity of the SCP. These results are consistent with several other studies and appear to be in part suggestive of Andreasen's proposed cortico-cerebellar-thalamic-cortical (CCTCC) circuit for schizophrenia⁹. This study suggests that gross anatomical abnormalities play a role either in the pathogenesis or development of the illness. We did not, however, replicate other documented findings: most significantly the often-reported finding of decreased FA in the temporal lobe and the corpus callosum¹⁰. Finally, we report an area of significantly increased FA in the subject population corresponding to occipital projections of the corpus callosum. This is, to the best of our knowledge, a previously unreported finding.

We also found that total PANSS score was robustly correlated bilaterally with FA in an anterior portion of the occipital lobe bordering on the parietal lobe. Neither SANS nor PANSS positive symptoms scores were found to be significantly correlated to FA.

References

1. Kubicki M, Mccarley R, Westin C, et al. A review of diffusion tensor imaging studies in schizophrenia. *Journal of Psychiatric Research* 2007;41:15–30. [PubMed: 16023676]
2. Szeszko PR, Robinson DG, Ashtari M, et al. Clinical and Neuropsychological Correlates of White Matter Abnormalities in Recent Onset Schizophrenia. *Neuropsychopharmacology*. 2007
3. Kubicki M, McCarley R, Westin CF, et al. A review of diffusion tensor imaging studies in schizophrenia. *J Psychiatr Res* 2007;41:15–30. [PubMed: 16023676]
4. Shin YW, Kwon JS, Ha TH, et al. Increased water diffusivity in the frontal and temporal cortices of schizophrenic patients. *Neuroimage* 2006;30:1285–1291. [PubMed: 16406258]
5. Smith SM, Jenkinson M, Johansen-Berg H, et al. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *Neuroimage* 2006;31:1487–1505. [PubMed: 16624579]
6. Basser PJ, Pierpaoli C. A simplified method to measure the diffusion tensor from seven MR images. *Magn Reson Med* 1998;39:928–934. [PubMed: 9621916]
7. Mori, SWS.; Nagae-Poetscher, LM.; van Zijl, PCM. *MRI Atlas of Human White Matter*. London: Elsevier Science; 2005.
8. Genovese CR, Lazar NA, Nichols T. Thresholding of statistical maps in functional neuroimaging using the false discovery rate. *Neuroimage* 2002;15:870–878. [PubMed: 11906227]
9. Andreasen NC. A unitary model of schizophrenia: Bleuler's "fragmented phrene" as schizencephaly. *Arch Gen Psychiatry* 1999;56:781–787. [PubMed: 12884883]

10. Hubl D, Koenig T, Strik W, et al. Pathways that make voices: white matter changes in auditory hallucinations. *Arch Gen Psychiatry* 2004;61:658–668. [PubMed: 15237078]

Table 1

DTI group difference and regression analysis results.

	MNI 152 coordinate			Tract	Cluster size ^d	FDR Threshold ^c	max Z score
	X	Y	Z ^a				
SCZ < CTRL	-13	0	60	R prefrontal cortical WM	5	4.51	5.74
	17	23	30	L anterior cingulate	7		5.89
	51	-38	18	L superior longitudinal fasciculus	7		5.54
	-8	-54	-17	R cerebellar dorsal intermediate zone WM	11		5.61
SCZ > CTRL	-3	49	-1	R forceps minor	6	3.63	5.03
PANSS Total ^b (n=11)	-20	-76	22	L forceps major	9	4.05	4.61
	29	-71	13	L forceps major	9		4.51
PANSS Positive Symptoms (n=11)	Non significant						
SANS (n=11)	Non significant						
Calgary ^b (n=10)	-7	-23	60	Premotor cortex WM.	4	4.08	5.11

^a MNI 152 coordinate represents the most significant voxel in a contiguous cluster of voxels.^b Positive correlation with FA^c Z statistic threshold for false discovery rate (FDR) threshold of 1% for primary measure and 5% for secondary (clinical and cognitive testing correlations)^d We report clusters of 3 or more contiguous significant voxels