Neuropsychopharmacology (2013) 38, 1954–1962

www.neuropsychopharmacology.org

Alterations of Superficial White Matter in Schizophrenia and Relationship to Cognitive Performance

Arash Nazeri[1], M Mallar Chakravarty[1,2,3,4,5], Daniel Felsky[1,2,6], Nancy J Lobaugh[2,3,6,7], Tarek K Rajji[3,4,6,8], Benoit H Mulsant[3,4,6,8] and Aristotle N Voineskos*[,1,2,3,4,6,8]

[1]Kimel Family Translational Imaging-Genetics Laboratory, Toronto, ON, Canada; [2]Research Imaging Centre, Toronto, ON, Canada; [3]Campbell Family Mental Health Institute, Centre for Addiction and Mental Health, Toronto, ON, Canada; [4]Department of Psychiatry, University of Toronto, Toronto, ON, Canada; [5]Institute of Biomaterials and Biomedical Engineering, University of Toronto, Toronto, ON, Canada; [6]Institute of Medical Science, University of Toronto, Toronto, ON, Canada; [7]Department of Neurology, University of Toronto, Toronto, ON, Canada; [8]Underserved Populations Program, Centre for Addiction and Mental Health, Toronto, ON, Canada

Post-mortem studies have demonstrated alterations in superficial white matter (SWM) in schizophrenia patients. Diffusion tensor imaging (DTI) can be used to assess SWM *in vivo*, and compare SWM fractional anisotropy (FA) in schizophrenia patients *vs* healthy controls. The assessment of SWM *in vivo* also provides an opportunity to identify novel neural correlates of cognitive performance, and potential cognitive impairment in schizophrenia patients. Forty-four patients with schizophrenia and 44 matched healthy controls underwent neuroimaging and cognitive protocols. Using an SWM mask and tract-based spatial statistics, differences in SWM-FA were examined between groups. SWM-FA clusters different between groups were then used to predict cognitive performance with multiple linear regression. The relative contribution of SWM fiber subtypes (deep white matter extensions *vs* U-fibers and intraregional fibers) from significantly different clusters was examined. Compared to controls, patients with schizophrenia had reduced FA in five SWM clusters: the largest a left posterior parieto-occipital cluster, followed by four clusters in the left frontal lobe. SWM-FA in the frontal lobe clusters predicted attention, working memory, and processing speed performance in healthy controls, but not in patients with schizophrenia. The majority of streamlines tracked from these clusters were restricted to U-fibers and intraregional fibers, rather than deep white matter extensions. Our analyses revealed prominent SWM disruption in patients with schizophrenia compared to controls. SWM–cognition relationships shown in healthy individuals were disrupted in patients with schizophrenia. SWM may be an important neurobiological substrate of cognitive performance and a novel cortical treatment target for cognitive deficits in schizophrenia patients.
Neuropsychopharmacology (2013) **38,** 1954–1962; doi:10.1038/npp.2013.93; published online 8 May 2013

Keywords: schizophrenia; diffusion tensor imaging; superficial white matter; cognitive impairment; U-fibers; tract-based spatial statistics

INTRODUCTION

To date, diffusion tensor imaging (DTI) studies in neuropsychiatric disorders have focused almost exclusively on long-range tracts within deep white matter. In schizophrenia patients, these studies have primarily found alterations of frontotemporal, interhemispheric and frontothalamic white matter tracts (McIntosh *et al*, 2008; Voineskos *et al*, 2010), inferred mainly from reductions in fractional anisotropy (FA), a measure of directional dependence of diffusion of water. These results have been generally interpreted to support the overarching theory of schizophrenia as a disconnection syndrome (Davis *et al*, 2003), as tracts in deep white matter form the substrates of long-range corticocortical white matter connectivity. Reduced FA in deep white matter tracts may contribute to cognitive dysfunction in schizophrenia patients (Perez-Iglesias *et al*, 2010; Voineskos *et al*, 2012). However, local connectivity is also very important for effective brain function (Fornito *et al*, 2012). Local white matter connections lie in superficial white matter (SWM). Although there are several published studies demonstrating SWM disruption in post-mortem schizophrenia brain (Akbarian *et al*, 1993; Eastwood and Harrison, 2005; Joshi *et al*, 2012), much less is known about SWM *in vivo* in patients with schizophrenia.

Lying just beneath the cortical ribbon, SWM is composed primarily of: (1) U-shaped association fibers, which form the major local white matter connections in the brain arching through the cortical sulci to connect adjacent gyri; (2) intracortical axons, which extend directly to white matter from the overlying gray matter; and (3) termination fibers from deep white matter pathways. Results from

*Correspondence: Dr AN Voineskos, Centre for Addiction and Mental Health, 250 College Street, Toronto, ON, Canada M5T 1R8, Tel: +1 416 535 8501 ext. 4378, Fax: +1 416 979 6936, E-mail: Aristotle.Voineskos@camh.ca
Received 19 December 2012; revised 14 February 2013; accepted 15 March 2013; accepted article preview online 16 April 2013

post-mortem SWM studies in schizophrenia patients have typically, although not always, shown altered interstitial white matter neuron density and distribution (Akbarian *et al*, 1996; Eastwood and Harrison, 2005), with increased density as the most common finding (Yang *et al*, 2011). To date, only one study has examined SWM *in vivo* in schizophrenia patients using a DTI-based approach (Phillips *et al*, 2011). In this study, left hemisphere temporal and occipital SWM-FA was affected in schizophrenia patients (Phillips *et al*, 2011), congruent with a primarily left-sided distribution of cortical deficits often reported in schizophrenia neuroimaging studies (Oertel-Knochel and Linden, 2011). In addition, first-degree relatives of schizophrenia patients shared similar SWM deficits to patients, providing support for a genetic role in the etiology of SWM deficits, and helping to rule out confounds such as medication effects. However, the findings from that study did not align with post-mortem schizophrenia data, which suggest that supporting SWM disruption is primarily in the frontal lobes (Yang *et al*, 2011), specifically within the prefrontal cortex. These prefrontal cortical regions are critical for attention, working memory, and executive control, cognitive domains that are impaired in schizophrenia patients (Ehrlich *et al*, 2012; Minzenberg *et al*, 2009).

We conducted a DTI study that examined SWM *in vivo*, and its relationship to cognitive function, in 44 patients with schizophrenia individually matched to 44 healthy control subjects. We used a novel FA-based skeletonized approach that measures SWM, based on a modification of tract-based spatial statistics (TBSS) (Smith *et al*, 2006). The TBSS approach minimizes errors associated with partial-volume effects and white matter tract alignment used in more traditional voxel-based methods (Smith *et al*, 2006). We had three main objectives: first, to determine whether we could obtain similar findings to the recent first DTI study of SWM in patients with schizophrenia using a larger sample of patients and controls and a novel image analysis method; second, to determine whether SWM regions that showed between-group differences were related to cognitive performance in healthy controls and patients with schizophrenia; and third, to conduct an exploratory analysis of SWM fiber subtypes (deep white matter extensions, U-fibers, and intraregional fibers) that might contribute to between-group differences, using probabilistic tractography. We hypothesized that we would replicate findings from the previous DTI study, by uncovering frontal SWM impairment in patients compared to controls. We also hypothesized that frontal SWM-FA would predict performance in frontally based cognitive tasks in healthy controls, but disruption of SWM in patients would lead to relationships with cognitive performance different from those predicted in controls.

MATERIALS AND METHODS

Participants

Participants were recruited at the Center for Addiction and Mental Health (CAMH) in Toronto, Canada, via referrals, study registries, and advertisements. All clinical assessments occurred at CAMH and MRI scans were performed at a nearby general hospital in Toronto. The study was approved by the Research Ethics Board of CAMH and all participants provided informed, written consent.

Community-dwelling outpatients ($n = 44$) with schizophrenia were individually matched based on age, sex, handedness, and highest parental years of education to healthy controls ($n = 44$). All participants were between 18 and 55 years of age. All participants were interviewed by a psychiatrist and were administered the Structured Clinical Interview for DSM-IV Disorders (First *et al*, 1995) to determine diagnosis and duration of illness. The Positive and Negative Syndrome Scale (Kay *et al*, 1987) was administered to further characterize illness symptoms. IQ was measured using the Wechsler Test for Adult Reading (Wechsler, 2001). Burden of comorbid physical illness was measured by the Cumulative Illness Rating Scale for Geriatrics (Miller *et al*, 1992). Medication histories were initially recorded based on self-reports, and then verified either by the patient's treating psychiatrist or chart review. All subjects received urine toxicology screens and anyone with current substance abuse or any history of substance dependence was excluded. Individuals with previous head trauma with loss of consciousness or neurological disorders were also excluded. For controls, a history of a primary psychotic disorder in first-degree relatives was also an exclusion criterion (Table 1).

Cognitive Testing

All subjects underwent a battery of cognitive tests administered over approximately 1.5 h. This battery included tasks that assess a wide range of cognitive domains in which impairment has been reported in schizophrenia patients (Rajji *et al*, 2009), namely executive function, working memory, attention, verbal fluency, verbal memory, visual memory, set-shifting, response inhibition, mental flexibility, spatial ability, and sensorimotor function. We explored the relationship of SWM integrity with the five cognitive domains with evidence for 'severe impairment' in schizophrenia patients, based on meta-analytic scores of 0.8 or more standard deviations below the normative standards (Dickinson *et al*, 2007; Fioravanti *et al*, 2005; Reichenberg, 2010): working memory (maintenance and manipulation), attention, processing speed, declarative memory, and executive function. In our cognitive battery, these domains were, respectively, assessed using the letter number sequence (LNS) task, the digit span, digit symbol coding, and story recall tasks from the Repeated Battery for the Assessment of Neuropsychological Status, and the Trails B test.

Image acquisition

T1-weighted imaging. High-resolution T1-weighted magnetic resonance images were acquired using an eight-channel head coil on a 1.5 T GE Echospeed system (General Electric Medical Systems, Milwaukee, WI). Axial 3D inversion recovery prepared spoiled gradient recall images were acquired using the following parameters: TR/TE/TI = 12.3/5.3/300; flip angle = 20°; NEX = 1; 124 contiguous images, and 1.5 mm slice thickness.

DTI. For DTI, a single-shot echo planar sequence was used with diffusion gradients applied in 23 non-collinear directions and $b = 1000\,s/mm^2$. Two $b = 0$ images were

obtained. Fifty-seven axial–oblique slices (parallel to AC–PC plane) were acquired for whole brain coverage. Slice thickness was 2.6 mm, and voxels were isotropic. The field of view was 330 mm and the size of the acquisition matrix was $128 \times 128\,mm^2$, with TR/TE = 15 000/85.5. The entire sequence was repeated three times to improve the signal-to-noise ratio.

Image Processing and Analyses

Diffusion data preprocessing. For each subject, all three repetitions were concatenated in the fourth dimension, motion and eddy current corrected, split back to the original volumes, and ultimately averaged using standard tools available from FSL v4.1 (www.fmrib.ox.ac.uk/fsl). Next, the FSL brain extraction tool was used (Smith, 2002), and finally, FA images were created by fitting a tensor model at each voxel to the averaged diffusion data using DTIFit (FMRIB's Diffusion Toolbox, implemented in FSL).

SWM mask and TBSS. SWM was defined in MNI space as a part of the white matter that is both adjacent to the cortex and is not included in any of the deep white matter regions of the ICBM-DTI-81 white matter labels atlas (http://cmrm.med.jhmi.edu/) (Mori *et al*, 2005). To create this SWM mask, FA images from all of the subjects were thresholded at 0.2–0.3, which mainly corresponds to the white matter that lies adjacent to the cortical areas, as shown recently (Oishi *et al*, 2008). A diffusion-weighted image was rigidly transformed to T1 images and each T1 image was nonlinearly transformed to MNI space using the Advanced Normalization Tools algorithm (Avants *et al*, 2008); the concatenation of these two transformations was used to transform FA images to MNI space. Next, individual binarized FA maps were averaged in the MNI space to create a probabilistic mask, which was then thresholded at 50%. As a conservative measure, the resulting binary mask was dilated by 2 mm from each direction. Finally, to address our second objective, the deep white matter regions from the ICBM-DTI-81 white matter labels atlas were removed from the resulting mask.

The TBSS pipeline was then used to analyze SWM-FA differences between our control and schizophrenia groups. First, all FA images were nonlinearly registered to the target image (FMRIB58_FA) provided by the FSL software. Next, the mean-FA image was created and the tracts were skeletonized to generate a white matter representation of the centers of all tracts common to all subjects. To discard non-white matter voxels, the FA threshold was set to 0.2. A local maximum FA, constrained by a search space, was then projected onto the skeleton. To account for residual misalignments and facilitate group-wise comparison, each individual's FA image is searched for local maximum value in the orthogonal to the skeleton. This local maximum was then projected onto the skeleton(Smith *et al*, 2006). Only voxels that were included in the SWM mask were retained for further analysis, and then compared between groups.

Finally, group comparisons between schizophrenia patients and their age/sex-matched healthy controls were carried out with permutation-based analysis, using 5000 random permutations. This was achieved with the *randomise* function implemented in FSL, utilizing threshold-free cluster-enhancement method (Smith and Nichols, 2009). Statistical maps were then thresholded at $p < 0.05$ fully corrected for multiple comparisons (family-wise error (FWE)-corrected).

SWM-FA and cognitive performance. Cognitive test results for each domain were compared between groups using independent samples *t*-tests. Then, for a given cognitive score (dependent variable), all significant clusters (independent variables) were screened using step-wise multiple linear regression analysis (using average FA values extracted from each cluster). The criteria used for each step were based on F-tests, with entry set at $p = 0.05$ and removal set at $p = 0.10$. This step was carried out separately in schizophrenia patients and in healthy subjects for each cognitive domain. Clusters that remained in the final regression models (either in schizophrenia- or healthy-only condition) were analyzed using a full factorial general linear model, which included cluster's mean FA and diagnosis to predict the given cognitive score in the whole sample.

A Bonferroni-corrected *p*-value of 0.01 (two-tailed) was used as the significance threshold ($\alpha = 0.05/5 = 0.01$) because of the use of five cognitive tests. Statistical analyses in this section were performed using SPSS v.17.0 for Windows (SPSS, Chicago, IL).

Exploratory probabilistic tractography. To interrogate relative contribution of U-fibers and/or intraregional fibers *vs* deep white matter extensions to significant voxels from each cluster, first the SWM mask was transformed to individual native space for each subject. Next, all voxels from each cluster from the TBSS results were used as seed points to perform two rounds of tractography. The total number of successful streamlines projected from a seed region is defined as the 'waytotal', as per the FSL website (http://fsl.fmrib.ox.ac.uk/fsl/fsl-4.1.9/fdt/fdt_probtrackx.html). For the first-level analysis, we calculated all streamlines, that is, the 'Free ($\text{waytotal}_{\text{Free}}$)' without any exclusion mask, and for the second-level analysis, we calculated the 'Constrained ($\text{waytotal}_{\text{Constrained}}$)', where fiber tracking was restricted by 1-SWM exclusion mask (ie, any streamline that exited the SWM mask was excluded). Finally, the percentage of streamlines restricted in SWM (ie, U-fibers and intraregional fibers) was measured for each cluster as follows:

$$\text{Tracts restricted to SWM} = (\text{waytotal}_{\text{Constrained}}/\text{waytotal}_{\text{Free}}) \times 100\% \quad (1)$$

Probabilistic fiber tracking discussed in this section was conducted for one cluster at a time, separately for each subject using bedpostX/probtrackX implemented in FMRIB's Diffusion Toolbox (FDT) (Behrens *et al*, 2003) (see Supplementary Materials and Methods).

RESULTS

SWM Mask and TBSS

The resulting SWM skeleton is shown in Figure 1. In the between-group analysis, schizophrenia subjects exhibited significantly reduced FA in SWM compared to controls

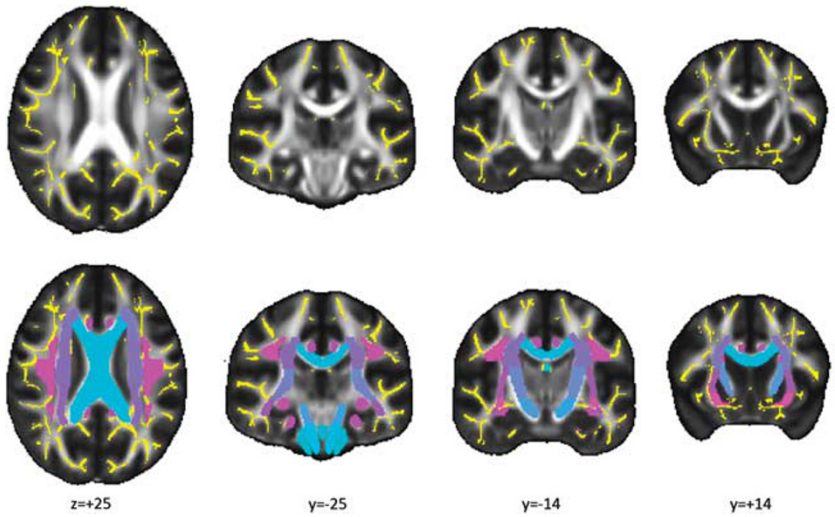

Figure 1 The top row demonstrates the final superficial white matter (SWM) skeleton mask (yellow) on different slices from the FMRIB58_FA standard-space. The bottom row shows the SWM skeleton mask in association with different deep white-matter labels (in purple spectrum) from Johns Hopkins University Diffusion Tensor Imaging Atlas that had been deleted from the skeleton. FA, fractional anisotropy.

(FWE-corrected, $p<0.05$) in five clusters (ie, contiguous sets of voxels) in the left hemisphere: (i) the largest cluster comprised a contiguous set of voxels stretching from the occipital lobe to the precuneus and posterior cingulate cortex (PCC); the remaining clusters were in the frontal lobe; (ii) inferior frontal and middle frontal gyri; (iii) lateral orbitofrontal cortex; (iv) precentral and inferior frontal gyri; and (v) frontal operculum and insular cortices. There was no single SWM voxel showing statistically significant increase in FA in patients with schizophrenia compared to controls (Figure 2 and Table 2). Re-analysis of the data without the left-handed subjects did not change the results.

SWM and Cognitive Performance

Schizophrenia patients performed significantly worse on all cognitive tests (Supplementary Table S1). Both main effects of SWM cluster FA in healthy subjects and diagnosis-by-cluster FA interactions in the entire sample were found (Figure 3). For LNS score (working memory), the mean FA value from the inferior and middle frontal gyrus cluster (cluster-2) passed the inclusion criteria (ie, uncorrected $p<0.05$) for screening multiple linear regression analysis ($\beta=0.32$, $p=0.037$) in healthy subjects. However, it neither showed a main effect ($F_{1,82}=0.097$, $p=0.76$) nor a significant diagnosis-by-cluster interaction ($F_{1,82}=5.12$, $p=0.025$) after correction for multiple comparisons. Similarly, for the digit span task (attention), mean FA of the inferior and middle frontal gyrus cluster (cluster-2) entered in the regression model to predict digit span forward ($\beta=0.452$, $p=0.002$) in the healthy subjects. However, it neither showed a significant main effect ($F_{1,84}=3.1$, $p=0.079$) nor a significant diagnosis-by-cluster interaction ($F_{1,84}=5.6$, $p=0.02$) after correction for multiple comparisons. For digit symbol coding (processing speed), the mean FA value extracted from the frontal operculum and insula cluster (cluster-5) significantly predicted performance ($\beta=0.5$, $p=0.001$) in the healthy subjects. It also demonstrated a significant interaction effect with diagnosis ($F_{1,87}=11.3$, $p=0.001$), but a nonsignificant main effect ($F_{1,87}=2.1$, $p=0.151$) in the final GLM. No SWM cluster passed the inclusion criteria to enter the GLM for prediction of story recall (delayed memory) and Trails B (executive function) performance.

Probabilistic Tractography

Overall, fiber tracking demonstrated a high percentage of streamlines (72.8%) that were completely comprised of U-shaped fibers and axonal fibers, rather than deep white matter connections from the five clusters that differed significantly between schizophrenia patients and healthy controls (Supplementary Table S2 and Figure S1).

DISCUSSION

We found reduced SWM-FA in patients with schizophrenia compared to healthy controls in five different clusters in the left hemisphere. The largest contiguous cluster (cluster-1) included SWM stretching from the occipital lobe to the precuneus within the parietal cortex and to the PCC. The other four clusters were located within the frontal lobe: in the inferior and middle frontal gyri, that is, ventro- and dorsolateral prefrontal cortex (cluster-2); in the lateral orbitofrontal cortex (cluster-3); in the premotor and motor cortex, mainly precentral gyrus (cluster-4); and in the frontal operculum over the insula, mainly pars opercularis (cluster-5). To our knowledge, our study was the first to examine the cognitive correlates of SWM-FA: SWM-FA in frontal clusters predicted cognitive performance in healthy subjects but not in patients with schizophrenia. Thus, frontal SWM disruption in schizophrenia patients may be related to cognitive impairment in this disorder. Our findings of deficits in cortical midline and left frontal SWM FA are neuroanatomically congruent with an accumulated body of work in schizophrenia patients,

Table 1 Demographic Characteristics of Patients with Schizophrenia and Matched Healthy Controls

	Patients with schizophrenia	Healthy controls	*p*-Value
Mean (SD)			
Age	36 (13)	37 (11)	0.793
Education	13 (2)	15 (2)	<0.0001
Parental education	14 (6)	15 (5)	0.40
IQ	107 (16)	117 (7)	0.0003
CIRS-G	2 (1)	1 (1)	<0.0001
BMI	26 (6)	25 (4)	0.36
Systolic BP	123 (15)	120 (13)	0.32
Diastolic BP	77 (10)	77 (10)	1
Age of onset	23 (5)	NA	
Duration of illness	14 (13)	NA	
Chlorpromazine eq. (mg)	328 (241)	NA	
PANSS		NA	
Positive	13 (5)		
Negative	14 (6)		
General	25 (7)		
N (44 in each group)			
Diagnosis	37 SZ, 7 SZA	NA	
Sex	30 M, 14 F	30 M, 14 F	1
Handedness	42 R, 2 L	42 R, 2 L	1
Ethnicity	33 C, 11 NC	37 C, 7 NC	0.29
Currently smoking	23	18	0.28
Antipsychotic treatment	4 First generation	NA	
	33 Second generation		
	3 Clozapine		
	7 None		

Abbreviations: C, caucasian; CIRS-G, Clinical Information Rating Scale; F, female; IQ, Wechsler Test for Adult Reading; L, left; M, male; NA, not applicable; NC, non-caucasian; PANSS, Positive and Negative Syndrome Scale; R, right; SZ, schizophrenia; SZA, schizoaffective disorder.

implicating disruption of deep white matter tracts connecting cortical midline structures, and connecting to the left frontal lobe. Finally, our exploratory fiber classification revealed that close to three-quarters of SWM voxels with reduced FA in schizophrenia patients belong to short range fibers rather than deep white matter extensions within SWM.

Cluster-1 comprised the single largest group of SWM voxels that showed reduced FA in patients with schizophrenia compared to controls. Cluster-1 included SWM in the superior lateral occipital cortex, the precuneus (which is located in parietal cortex), and PCC. Our occipital and parietal cortex finding replicates findings from the only other study to examine SWM in schizophrenia patients (Phillips *et al*, 2011) and this cluster comprises structures that form part of the default mode network. In particular, the precuneus and PCC form key hubs (Fransson and Marrelec, 2008; Greicius *et al*, 2003) of the default mode network, as posterior cortical midline structures (Raichle *et al*, 2001). This network refers to a set of brain regions that collectively deactivate during performance of attention-demanding tasks and are implicated in self-referential mental processing (Buckner *et al*, 2008; Raichle *et al*, 2001). Multiple lines of evidence now implicate default mode network disruption in schizophrenia (for a review see Whitfield-Gabrieli and Ford, 2012): reduced task-related suppression within default mode network components has been consistently reported during a broad range of mental processes in patients with schizophrenia (Meyer-Lindenberg *et al*, 2005; Whitfield-Gabrieli *et al*, 2009). Given the proximity of SWM to the overlying gray matter, it is possible that disruption of SWM integrity connecting the precuneus and PCC to adjacent structures may partly account for reported alterations in default mode network dynamics, and altered functional network connectivity in schizophrenia patients (Yu *et al*, 2011). The highest density of interstitial white matter neurons is in the SWM immediately subjacent to the cortical gray matter. The large population of interstitial white matter neurons in the SWM exists as both vasodilators (nitric oxide synthase positive) and vasoconstrictors (neuropeptide-Y positive), with colocalization of both types of neurons. Thus, these neurons form part of the neural system involved in the coupling of cortical microvessels to neuronal activity (Defelipe *et al*, 2010). Therefore, in patients with schizophrenia, alterations in SWM-FA in default mode regions, such as precuneus and PCC, may contribute to functional connectivity differences in the same neuroanatomical regions.

Decreased SWM-FA in schizophrenia patients was also present in the left lateral prefrontal cortex, specifically ventro- and dorsolateral regions (ie, inferior and middle frontal gyri) (cluster-2). Here, our findings align with post-mortem data supporting SWM disruption in schizophrenia in the dorsolateral prefrontal cortex (DLFPC) (Yang *et al*, 2011) showing: (i) an increase in interstitial white matter neuron density; (ii) a greater density of interstitial white matter neurons in left DLPFC compared to right DLPFC; and (iii) a correlation between the increased density of these neurons with a gray matter interneuron deficit. This is consistent with evidence suggesting that some interstitial white matter neurons may be remnants of the subplate (Chun and Shatz, 1989) as GABAergic neurons that tangentially migrated from the ganglionic eminence during cortical development (Yang *et al*, 2011). Functional imaging studies have consistently implicated dysfunction of ventro- and dorsolateral PFC—essential structures for higher-order cognitive processing—as an important neural substrate for cognitive dysfunction in schizophrenia, particularly during working memory tasks (Dreher *et al*, 2012; Eisenberg and Berman, 2010). Our regression model showed that the inferior and middle frontal gyrus cluster (cluster-2) FA predicted attention and working memory performance in healthy controls, supporting the fact that SWM in ventro- and dorsolateral PFC have a role in attention and working memory performance in healthy controls. However, this relationship was not significant in patients with schizophrenia, suggesting a potential disruption in an SWM-FA—cognitive performance relationship.

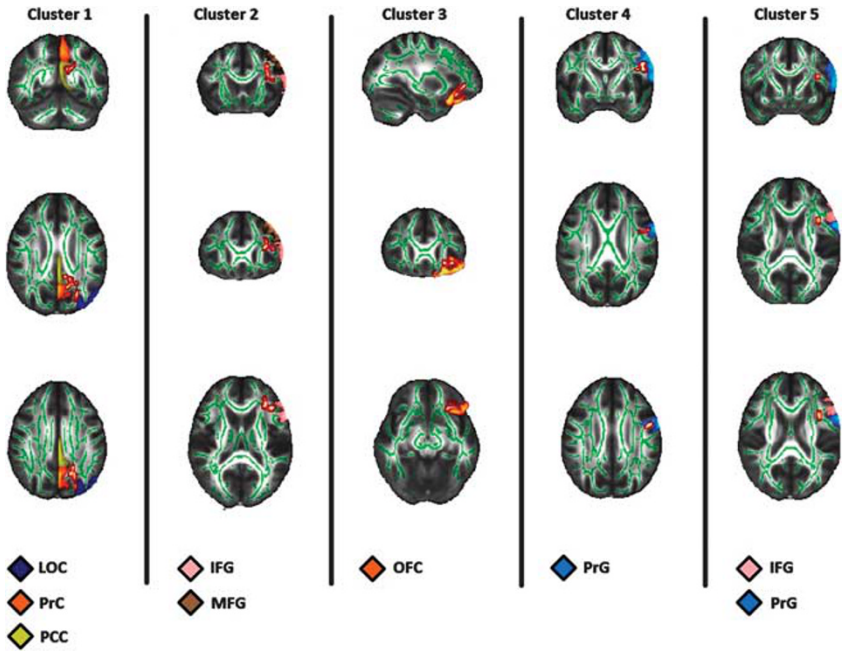

Figure 2 Clusters from tract-based spatial statistical analysis showing decreased fractional anisotropy (FA) in the patients with schizophrenia compared to healthy controls ($p_{FWE} < 0.05$). On the FMRIB58_FA standard-space image (gray scale), the white matter skeleton is projected (green). Some of the associated cortical regions from the Harvard Oxford Cortical Atlas are also demonstrated. IFG, inferior frontal gyrus; LOC, lateral occipital cortex (superior division); MFG, middle frontal gyrus; PCC, posterior cingulate cortex; PrC, precuneus; PrG, precentral gyrus.

Table 2 MNI Coordinates, Volume, and Associated Cortical Regions of Superficial White Matter Clusters with Decreased Fractional Anisotropy Values in Patients with Schizophrenia and Healthy Controls

Cluster	MNI coordinates[a]			Volume (mm^3)	Mean cluster FA (SD)		Minimum $p_{FWE\text{-}corr}$	Lobe	Associated cortical regions[b]
	X	Y	Z		HC	Schz			
1	−16	−57	30	803	0.46 (0.031)	0.43 (0.029)	0.007	Occipital	LOC, PrC, PCC, SCC
2	−30	25	17	446	0.42 (0.029)	0.38 (0.028)	0.028	Frontal	IFG (pars triangularis and pars opercularis), MFG
3	−34	27	−9	276	0.35 (0.032)	0.32 (0.037)	0.031	Frontal	OFC
4	−44	−2	31	146	0.47 (0.034)	0.43 (0.036)	0.029	Frontal	PrG
5	−36	8	19	27	0.53 (0.044)	0.50 (0.039)	0.049	Frontal	PrG, FOC; IFG (pars opercularis)

Abbreviations: FOC, frontal operculum cortex; IFG, inferior frontal gyrus; LOC, lateral occipital cortex (superior division); MFG, middle frontal gyrus; OFC, frontal orbital cortex; PCC, posterior cingulate cortex; PrC, precuneus; PrG, precentral gyrus; SCC, supracalcarine cortex.
[a]Given that these clusters lie in the superficial white matter subjacent to cortex, coordinates may be lower in magnitude than expected for their cortical counterparts.
[b]All cortical regions associated with clusters from the between-group tract-based spatial statistical analysis were located in the left hemisphere.

Cluster-3 (orbitofrontal cortex) and cluster-4 (precentral gyrus) also showed reduced FA in patients with schizophrenia compared to healthy controls. These findings are congruent with several lines of investigation that show abnormalities of these regions in schizophrenia (Nakamura *et al*, 2008; Tanskanen *et al*, 2010). Cluster-5 (insula/frontal operculum) showed both reduced FA and a strong relationship with performance on the digit symbol coding task (a measure of processing speed and visual attention), as well as a diagnosis-by-cluster interaction showing disruption of this relationship in schizophrenia patients compared to controls. The anterior insula serves as an attentional switch between the default mode network and the attentional control network (Menon and Uddin, 2010); it is linked to the posterior parietal cortex and is a key node for self-awareness and self-referential tasks. The resting state network is negatively correlated with the insula (along with supplementary motor area—cluster-4) (Fox *et al*, 2005). Overall, these findings suggest that cluster-5 form part of the attentional network that is anticorrelated with the default mode network during the resting state, and structural (Gerretsen *et al*, 2012) and functional (Bassett *et al*, 2008) evidence for insula disruption is present in schizophrenia patients. Furthermore, schizophrenia patients and their first-degree relatives consistently show poorer performance on the digit symbol coding task

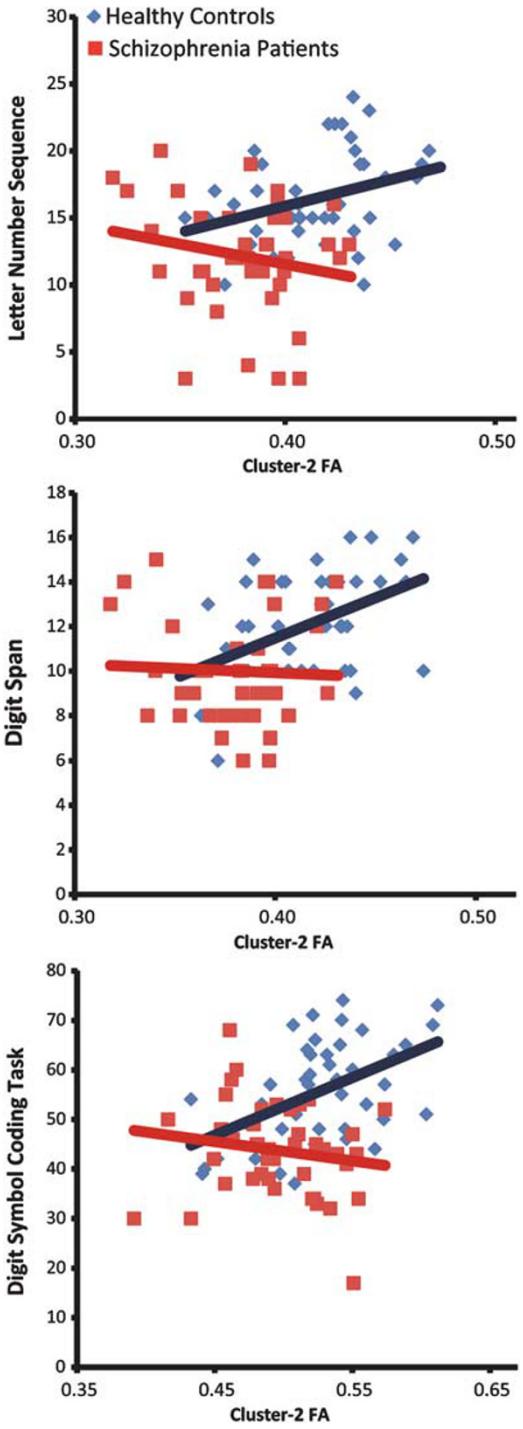

Figure 3 Relationships between mean fractional anisotropy values extracted from clusters (horizontal axis) and scores on specific cognitive tasks (vertical axis). Red squares and blue diamonds represent patients with schizophrenia and healthy controls, respectively.

(Dickinson *et al*, 2007). The neurobiology of impairment on this task has been hypothesized to be due to impaired communication or relay function in the brain of schizophrenia patients, consistent with the role of the insula as a relay center in the brain.

Finally, we explored the underlying neuroanatomy that might contribute to differences in SWM between patients with schizophrenia and healthy controls: we used a probabilistic tractography algorithm to determine the relative contributions of U-shaped white matter fibers and intraregional white matter fibers compared to extensions of the deep white matter fibers. We found that almost three-quarters of SWM voxels within the five clusters that differed between the two groups were comprised of U-shaped and intraregional fibers rather than extensions of the deep white matter fibers. Although preliminary, our finding is congruent with the post-mortem data showing that disruption of SWM in schizophrenia patients is due to changes in interstitial white matter neuron in U-shaped and intraregional fibers. *In vivo*, greater appreciation of the neuroanatomy of U-shaped fibers is increasing (Catani *et al*, 2012), and more work is necessary to clarify the role of these structures in neuropsychiatric disorders, and their functional importance.

Strengths and limitations of our study should be considered in the context of the unique published *in vivo* SWM study in the schizophrenia and the post-mortem SWM literature. First, the measurement of SWM-FA *in vivo* is a novel way to assess white matter that is typically not a focus of other DTI studies. Our findings partially replicate those of Phillips *et al* (2011) and they provide new insights into the importance of SWM changes in schizophrenia patients and their relationship with cognitive deficits. An important difference between the two studies is our finding of SWM-FA reductions primarily in the left frontal lobe. This finding is consistent with several post-mortem studies also demonstrating disruption in SWM in the left frontal lobe in schizophrenia patients (Akbarian *et al*, 1993; Eastwood and Harrison, 2005). Methodological differences between the study of Phillips *et al* (2011) and our study may also account for differences in the results: our sample size (44 *vs* 26 patients with schizophrenia), our TBSS registration algorithm (*vs* surface-based registration), and our number of directions in DTI acquisition (23 *vs* 6). We cannot rule out the possibility that the changes we observed were due to medication effects or were epiphenomena of having a severe mental illness. However, the specific localization of our findings (including the lateralization to the left hemisphere) decreases the possibility that our findings are due to *medication* effects. We obtained >20 unique sampling orientations for a robust measurement of anisotropy (Jones, 2004). However, for robust estimations of tensor orientation and mean diffusivity at least 30 unique sampling orientations are required (Jones, 2004). Finally, the reductions in SWM-FA observed occurred underneath gray matter regions implicated within the default mode network or anticorrelated with it. In future studies, obtaining both resting state fMRI data and SWM-FA in the same subjects will allow to model directly the relationship between the two measures.

In summary, we found reductions in SWM-FA in patients with schizophrenia compared to healthy controls. These reductions were found in regions partially overlapping with a posterior default mode network as well as frontal SWM regions, all in the left hemisphere. Relationships observed between SWM-FA and cognitive performance in healthy controls were disrupted in patients with schizophrenia, providing support for the role of SWM-FA in cognitive deficits that have been robustly characterized (processing

speed, attention, and working memory) in schizophrenia patients. Our findings are congruent with a smaller recent neuroimaging study and post-mortem data; furthermore, our results provide novel biomarkers of core cognitive deficits in schizophrenia patients that could be the target for new treatments.

ACKNOWLEDGEMENTS

This work was supported by the Canadian Institutes of Health Research, Ontario Mental Health Foundation, the Brain and Behavior Research Foundation (formerly known as NARSAD), the Centre for Addiction and Mental Health (CAMH), and the CAMH Foundation through the Kimel Family, Koerner New Scientist Award, and Paul E Garfinkel New Investigator Catalyst Award. No sponsor or funder played any role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

DISCLOSURE

Dr Mulsant currently receives research support from Bristol-Myers Squibb (medications for a NIH-funded clinical trial) and Pfizer (medications for a NIH-funded clinical trial). He directly owns stocks of General Electric (<$5000). Within the past 3 years, he has also received some travel support from Roche.

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Supplementary Information accompanies the paper on the Neuropsychopharmacology website (http://www.nature.com/npp)