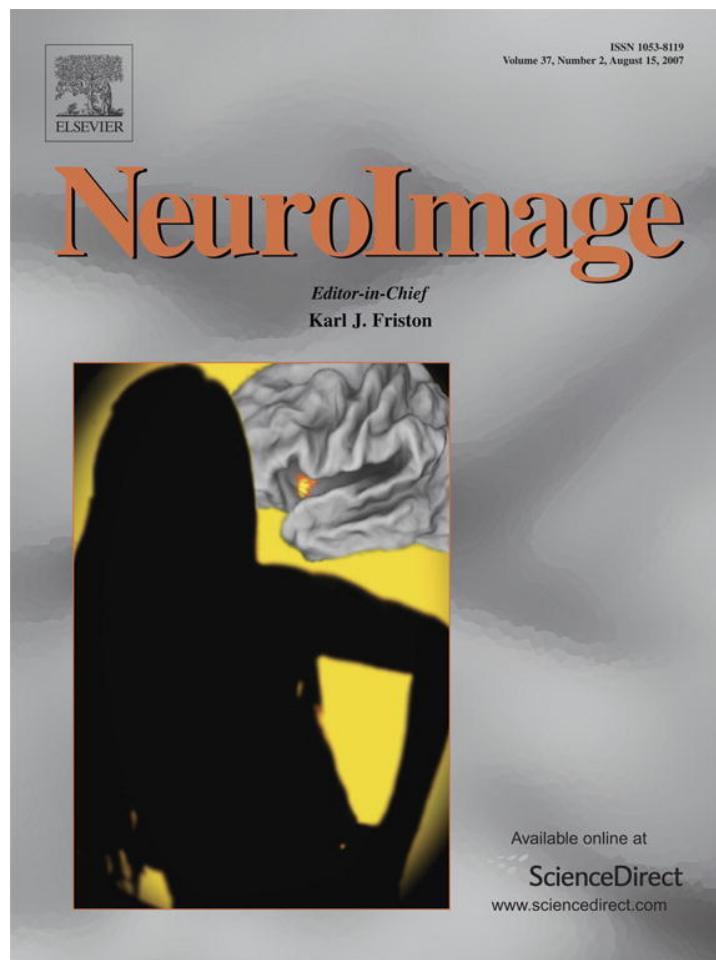


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Reduced microstructural integrity of the white matter underlying anterior cingulate cortex is associated with increased saccadic latency in schizophrenia

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The anterior cingulate cortex (ACC) is a key component of a network that directs both spatial attention and saccadic eye movements, which are tightly linked. Diffusion tensor imaging (DTI) has demonstrated reduced microstructural integrity of the anterior cingulum bundle as indexed by fractional anisotropy (FA) in schizophrenia, but the functional significance of these abnormalities is unclear. Using DTI, we examined the white matter underlying anterior cingulate cortex in schizophrenia to determine whether reduced FA is associated with prolonged latencies of volitional saccades. Seventeen chronic, medicated schizophrenia outpatients and nineteen healthy controls had high-resolution DTI scans. FA maps were registered to structural scans and mapped across participants using a surface-based coordinate system. Cingulate white matter was divided into rostral and dorsal anterior regions and a posterior region. Patients showed reduced FA in cingulate white matter of the right hemisphere. Reduced FA in the white matter underlying anterior cingulate cortex, frontal eye field, and posterior parietal cortex of the right hemisphere was associated with longer saccadic latencies in schizophrenia, though given the relatively small sample size, these relations warrant replication. These findings demonstrate that in schizophrenia, increased latency of volitional saccades is associated with reduced microstructural integrity of the white matter underlying key cortical components of a right-hemisphere dominant network for visuospatial attention and ocular motor control. Moreover, they suggest that anterior cingulate white matter abnormalities contribute to slower performance of volitional

saccades and to inter-individual variability of saccadic latency in chronic, medicated schizophrenia.

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Keywords: Anterior cingulate cortex; Antisaccade; Cingulum bundle; Diffusion tensor imaging; Schizophrenia; White matter

The anterior cingulate cortex (ACC) is a key participant in the direction of both spatial attention (Mesulam, 1981) and eye gaze, which are tightly linked (Hunt and Kingstone, 2003; Klein and McCormick, 1989). In neuroimaging studies, the ACC shows increased activation when ocular motor control is required, including on prosaccade and antisaccade tasks. Prosaccades are a prepotent response of looking towards a suddenly appearing visual target. Antisaccades require inhibition of the prepotent prosaccade and the generation of the novel behavior of looking away from a target. The ACC shows increased activation during prosaccades compared to fixation (Brown et al., 2006), greater activation for antisaccades than prosaccades (e.g., Brown et al., 2006; Doricchi et al., 1997; Ford et al., 2005; Manoach et al., 2007; Paus et al., 1993), and reduced activity in association with deficient anti-saccade performance in schizophrenia (Crawford et al., 1996). Specifically, the posterior part of the dorsal ACC has been labeled the ‘cingulate eye field’ on the basis of its involvement in tasks requiring volitional, but not reflexive saccadic control (Gaymard et al., 1998; Paus et al., 1993; Pierrot-Deseilligny et al., 2004). Lesions of the posterior dorsal ACC increase antisaccade errors (Milea et al., 2003) and prolong the latencies of both pro- and antisaccades (Gaymard et al., 1998). Schizophrenia is characterized

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by abnormal performance of volitional saccades (e.g., Calkins et al., 2003; Harris et al., 2006; Radant et al., 2007) and both functional and structural abnormalities of the ACC (for reviews, see Benes, 2000; Holcomb, 2004). In a previous study we reported significant slowing of correct prosaccade and antisaccade trials, demonstrating that in schizophrenia, even correct volitional saccades are abnormal (Manoach et al., 2002). In the present study, using the same saccadic paradigm, we investigated whether abnormalities of the white matter (WM) underlying dorsal ACC might contribute to the slowing of correct volitional saccades.

We focus on the ACC because unlike other key cortical components of the ocular motor network (i.e., frontal, parietal, and supplementary eye fields) (McDowell and Clementz, 2001), there is abundant evidence of both structural and functional abnormalities of the ACC in schizophrenia. Moreover, functional MRI evidence suggests that the ACC contributes to performance of our saccadic task in healthy individuals (Polli et al., 2005a), while showing abnormal activity in schizophrenia (Polli et al., 2005b). In addition to reports of ACC gray matter reductions in schizophrenia (e.g., Goldstein et al., 1999; Ha et al., 2004; Kuperberg et al., 2003; Mitelman et al., 2005; Ohnuma et al., 1997; Sigmundsson et al., 2001; Suzuki et al., 2002; Yamasue et al., 2004), there is evidence of volume reductions in the underlying WM (McDonald et al., 2005; Mitelman et al., 2005), and histopathological evidence of disturbances in micro- and macrocircuitry that might alter communication between the ACC and connected regions (for reviews, see Benes, 1993, 2000).

We examined the microstructural integrity of the WM underlying ACC using diffusion tensor imaging (DTI). DTI is an MRI technique that can detect white matter pathology in vivo. DTI was used to index the fractional anisotropy (FA) of water diffusion, which reflects the degree of directional coherence of water diffusion in tissue. While FA correlates with axon myelination (Harsan et al., 2006), not all of the biophysical determinants of WM diffusion anisotropy are fully understood (Beaulieu, 2002). Consistent with other evidence of ACC WM abnormalities in schizophrenia, previous DTI studies have found reduced FA of the cingulum bundle, the WM tract that underlies cingulate cortex (Ardekani et al., 2003; Hao et al., 2006; Kubicki et al., 2003; Sun et al., 2003; Wang et al., 2004), although there are also several negative reports (Agartz et al., 2001; Buchsbaum et al., 1998; Burns et al., 2003; Foong et al., 2002). Various factors may contribute to these discrepancies, such as differences in sample composition with regard to course of illness and/or medication regimen. Given the lack of standard methods for DTI acquisition and analysis, methodological differences likely play an important role (Jones et al., 2005; Kanaan et al., 2005).

Some previous DTI studies of the cingulum bundle in schizophrenia employed voxel-based analyses that depend on registering brains to a particular atlas, averaging across participants, and then testing for group differences at each voxel (e.g., Agartz et al., 2001; Ardekani et al., 2003; Buchsbaum et al., 1998; Foong et al., 2002). Healthy individuals show a high degree of inter-subject variability of brain morphology, particularly in regions involved in higher cognitive function (Brett et al., 2002; Rajkowska and Goldman-Rakic, 1995), and in schizophrenia variability is even greater (Park et al., 2004a). Morphologic variability can confound inter-group comparisons of registered data as it may result in the averaging of disparate brain regions, which could artifactually lower and/or lead to greater variability of FA

measurements, which depend on the organizational coherence of WM. Defining regions of interest (ROIs) in the unregistered images of individual participants avoids the problems of inter-subject registration, but results may differ depending on which portion of the cingulum is sampled. Several studies used geometric (e.g., spherical or rectangular) ROIs placed on slices in the anterior and/or posterior cingulum (Burns et al., 2003; Sun et al., 2003; Wang et al., 2004) while another study sampled only the middle cingulum since the most anterior and posterior portions are affected by a high degree of curvature that can confound the measurement of FA (Kubicki et al., 2003). If cingulum abnormalities are confined to specific subregions, selective sampling may miss group differences.

The present study employed high-resolution DTI and cortical surface-based analyses (Dale et al., 1999; Fischl et al., 1999a) to investigate the microstructural integrity of cingulate white matter in schizophrenia. High-resolution DTI acquisition enabled accurate measurements of FA in the WM underlying the entire cingulate gyrus in spite of the high degree of curvature. This avoids biases inherent in sampling only from selected regions. The primary analyses involved defining ROIs based on anatomical landmarks in individual participants, measuring FA in the WM underlying each vertex (surface equivalent of voxel), averaging FA values across vertices in each ROI for each participant, and comparing groups.

We complemented the ROI analyses with vertex-wise analyses. This involved surface-based inter-subject registration and group comparisons of FA at every vertex of the registered data. Unlike volumetric approaches that rely only on intensity information, surface-based registration employs a non-rigid alignment algorithm to explicitly align cortical folding patterns and should be relatively robust to inter-individual differences in the gyral and sulcal anatomy of cingulate cortex (Dale et al., 1999; Fischl et al., 1999a). While surface-based procedures have been extensively applied in functional magnetic resonance imaging studies and to measure cortical thickness (e.g., Kuperberg et al., 2003; Rosas et al., 2002), this is the first application to DTI.

We divided the cingulate cortex into anterior and posterior segments and the anterior segment was further divided into rostral and dorsal regions. This division is based on differences in cytoarchitecture, function, and connectivity (Bush et al., 1998, 2000; Devinsky et al., 1995; Vogt et al., 1979; Whalen et al., 1998). Although previous work primarily implicates anterior cingulate in schizophrenia (Benes, 2000; Holcomb, 2004; Kerns et al., 2005; Laurens et al., 2003; Tamminga et al., 2000), we also investigated the WM of the posterior cingulate to determine the regional specificity of FA reductions and because several recent studies report posterior cingulate cortex abnormalities (Mitelman et al., 2005; Shimizu et al., 2007; Suzuki et al., 2005).

We expected to find FA reductions in anterior cingulate WM in schizophrenia and wanted to determine whether reduced FA, specifically in the WM underlying dorsal ACC, was associated with prolonged latencies of correct volitional saccades. Individual differences in cognitive processing speed have been proposed to reflect WM physiology, particularly myelination (e.g., Luciano et al., 2004), based on the well-established role of WM myelin thickness and axon diameter in determining conduction velocity. Recent reports of relations between FA (which reflects myelination (Harsan et al., 2006) and other WM microstructural properties (Beaulieu, 2002)) and cognitive reaction time lend indirect support to this proposal (Madden et al., 2004; Nestor et al., 2007; Tuch et al., 2005). On this basis, we reasoned that dorsal ACC WM micro-

structure might contribute to volitional saccadic latency, and that microstructural abnormalities, by impairing communication in the ocular motor network, could contribute to prolonged latencies in schizophrenia. Because prosaccade and antisaccade trials were presented in a pseudorandom sequence, both trial types required vigilance to instructional cues and task switching. Thus, the prosaccade trials of the present study were not purely 'reflexive', rather they were cognitively demanding volitional saccades. In summary, we expected that reduced FA in the WM underlying dorsal ACC would be related to prolonged latencies of volitional prosaccades and antisaccades in schizophrenia, as might be expected based on a previous lesion study (Gaymard et al., 1998).

Methods

Participants

(Table 1 provides demographic information.) The schizophrenia sample was comprised of 17 chronic outpatients recruited from an urban community mental health center, who had been maintained on stable doses of a variety of atypical antipsychotic medications for at least 6 weeks. Diagnoses were confirmed with Structured Clinical Interviews for DSM-IV (First et al., 1997). Clinical status was characterized with the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962), the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983). Nineteen healthy control participants, without a personal history of psychiatric illness or a family history of schizophrenia spectrum disorders, were recruited from the community with poster advertisements.

Participants were screened to exclude substance abuse or dependence within the past 6 months, a history of head injury resulting in a sustained loss of consciousness and/or cognitive sequelae, neurological illness, and any disorder affecting cerebral metabolism. All participants endorsed strong right-hand preference as determined by a laterality score of 70 or above on the modified Edinburgh Handedness Inventory (White and Ashton, 1976). The groups did not differ with regard to age, sex, handedness, or parental socioeconomic status (Hollingshead, 1965). Participants gave written informed consent. The study was approved by institutional review

Table 1
Means, standard deviations, and group comparisons of demographic data and rating scale scores

| Subject characteristics | Healthy subjects (<i>n</i> = 19) | Schizophrenia subjects (<i>n</i> = 17) | <i>t</i> | <i>p</i> |
|---------------------------|--------------------------------------|--|-------------------|----------|
| Age | 36 ± 13 | 41 ± 12 | 1.27 | 0.21 |
| Sex | 12M/7F | 13M/4F | $\phi = 0.14$ | 0.39 |
| Handedness (Edinburgh) | 92 ± 10 | 86 ± 19 | 1.27 | 0.21 |
| Parental SES ^a | 2.1 ± 1.2 | 2.6 ± 1.0 | <i>z</i> = 1.4 | 0.17 |
| Age of onset | | 24.5 ± 7.0 | | |
| Length of illness (years) | | 16.7 ± 10.2 | | |
| | | | Level of severity | |
| BPRS | | 15.5 ± 8.2 | Minimal | |
| PANSS positive | | 13.0 ± 5.4 | Mild | |
| PANSS negative | | 16.8 ± 6.2 | Mild | |
| SANS | | 32.7 ± 16.2 | Questionable | |

^a A lower score denotes higher status.

boards at Massachusetts General Hospital and the Massachusetts Department of Mental Health.

Image acquisition

Head stabilization was achieved with cushioning and participants wore earplugs to attenuate scanner noise. Images were collected using a 3.0-T Siemens Trio MRI scanner (Siemens Medical System, Iselin, NJ). Automated shimming procedures were performed and scout images were obtained. Two high-resolution structural images were acquired in the sagittal plane for slice prescription, spatial normalization (spherical and Talairach), and cortical surface reconstruction using a high-resolution 3D magnetization prepared rapid gradient echo (MPRAGE) sequence (repetition time (TR), 2530 ms; echo spacing, 7.25 ms; echo time (TE), 3 ms; flip angle 7°) with an in-plane resolution of 1 mm and 1.3 mm slice thickness. Single-shot EPI DTI was acquired using a twice refocused spin echo sequence (Reese et al., 2003) with the following sequence parameters: TR/TE = 8400/82 ms; *b* = 700 s/mm²; NEX = 1; ten T2 images acquired with *b* = 0; 72 diffusion directions; 128 × 128 matrix; 2 × 2 mm in-plane resolution; 64 axial oblique (AC-PC) slices; 2-mm (0 mm gap) slice thickness; scan duration 12'44". The *n* = 72 diffusion directions were obtained using the electrostatic shell algorithm (Jones, 2004).

Acquisition of behavioral data

Saccadic latency and directional accuracy measurements were acquired during magnetoencephalography scanning using electrooculography. Two bipolar pairs of EOG electrodes were placed to capture vertical and horizontal eye movements and blinks. The signals were sampled at 600 Hz. The saccadic task stimuli were generated using the Vision Shell programming platform (www.visionshell.com) and presented with a Digital Light Processing (DLP Infocus 350) projector onto a back-projection screen placed 102 cm in front of the subject. The task consisted of a pseudorandom series of prosaccade and antisaccade trials with randomly interspersed fixation intervals of 2, 4, or 6 s. Saccadic trials were balanced for right and leftward movements. Fig. 1 provides a graphic depiction of the task and a description of task parameters. Participants performed eight runs of the task, with short rests between runs. Each run lasted 5 min 22 s. The total experiment lasted about 1 h and generated a total of 278 prosaccade 285 antisaccade trials and 107 fixation intervals.

Scoring and analysis of eye movement data

EOG data were scored in MATLAB (Mathworks, Natick, MA) using a partially automated program that determined the directional accuracy of each saccade with respect to the required response and the latency from target onset. For each trial, saccadic onset was defined as the point preceding peak velocity at which the horizontal eye-position trace deviated from fixation (Fig. 1). To determine this point an automated algorithm started at the point of peak velocity and searched the eye-position trace backwards to fixation. Fixation was defined as the time point at which the slope of the eye-position trace was zero as determined by evaluating the slope in relation to the two preceding time points, a moving window of 5 ms. Algorithm results were visually inspected to ensure accuracy. Only trials with saccades in the desired direction and latencies between 130 and 800 ms were considered correct, and only correct saccades were included in the latency analyses. The cutoff of 130 ms excluded anticipatory saccades, which are

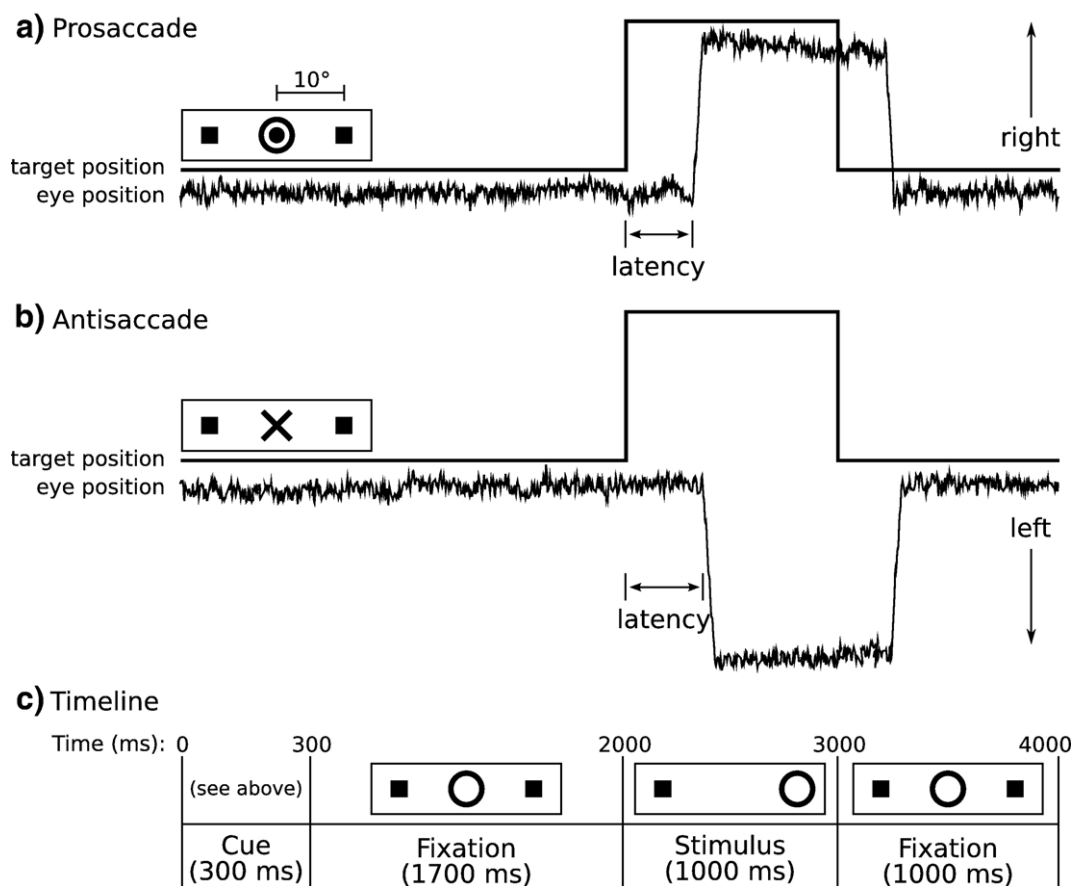


Fig. 1. Saccadic paradigm. Saccadic trials lasted 4000 ms and began with an instructional cue at screen center. For half of the participants, an orange ring was the cue for a PS trial and a blue X the cue for an AS trial. These cues were reversed for the rest of the participants. The cue was flanked horizontally by two small green squares of 0.2° side that marked the potential locations of stimulus appearance, 10° left and right of center. These squares remained on the screen for the duration of each run. At 300 ms the instructional cue was replaced by a green fixation ring at screen center with a diameter of 0.4° and luminance of 20 cd/m^2 . After 1700 ms the ring shifted to one of the two stimulus locations, right or left, with equal probability. This ring was the stimulus to which participants responded. The green ring remained in the peripheral location for 1000 ms and then returned to the center where participants were instructed to return their gaze for 1000 ms. Fixation intervals were simply a continuation of the fixation display that constituted the final second of the previous saccadic trial.

executed too quickly to be a valid response to the appearance of the target (Doricchi et al., 1997; Fischer and Breitmeyer, 1987; Straube et al., 1999). Trials with eye blinks (defined as vertical peak-to-peak EOG amplitude exceeding $200 \mu\text{V}$) prior to saccadic response were rejected from further analysis.

DTI analysis

The objective of the DTI analysis was to measure and conduct group comparisons of FA in the WM underlying specific regions. We relied primarily on ROI analyses that were based on individual anatomy. We complemented ROI analyses with a vertex-wise analysis of registered group data. For both analyses, FA was measured in the undeformed WM 2 mm below the WM/gray matter boundary. This strategy minimizes partial volume contributions from cortical gray matter and preserves regional specificity.

DTI data were analyzed using the following multi-step procedure (detailed below): (1) motion/eddy current distortion correction; (2) tensor reconstruction; (3) registration of FA and T1 volumes; (4) projection of subcortical FA values onto the WM/gray matter interface; (5) and group comparisons of average FA values in ROIs based on the unregistered data of each participant (ROI analysis). The vertex-wise analysis involved the following additional steps: (6)

registration of surface FA maps across participants and (7) group comparisons of FA values of the WM underlying each vertex on the cortical surface.

(1) The raw diffusion data were corrected for head motion and residual eddy current distortion by registering all images to the first T2 image, which was acquired with $b=0$. The registration was performed using the FLIRT tool (Jenkinson and Smith, 2001) from the FSL software library (<http://www.fmrib.ox.ac.uk/fsl>). The registration used a global affine (12 degrees of freedom) transformation, a mutual information cost function, and sinc resampling. (2) The diffusion tensor and FA volumes were then reconstructed using the standard least squares fit to the log diffusion signal (Basser et al., 1994).

(3) FA volumes were registered to the high-resolution structural (T1) volumes for each participant using the T2 volume as an intermediary. The T2 volume was taken from the $b=0$ image in the DTI acquisition and was therefore in register with the FA volume. The T2 intermediary was employed (a) to avoid potential bias that might arise from using the FA volume in the registration, since FA is the variable of interest and (b) because the gray/white boundary in the T1 volume has better correspondence with the T2 volume than the FA volume, allowing for a more accurate registration.

Each participant's averaged T2 volume was manually registered to the T1 volume with Tkregister2 (<http://surfer.nmr.mgh.harvard.edu>) using 9 degrees of freedom including translation, rotation, and scaling. Manual registration was used to (a) maximize anatomic agreement along the medial wall and (b) because echo planar imaging susceptibility distortions in DTI can confound global registration procedures. The resulting spatial transformation was applied to the FA volume, thus bringing the FA and T1 volumes into register.

(4) For each participant, a surface representation of the WM/gray matter boundary was derived from the T1 volume using a previously described segmentation, surface reconstruction, and inflation algorithm (Dale et al., 1999; Fischl et al., 1999a). FA was sampled in the WM 2 mm below the WM/gray matter boundary for each vertex on the surface and then projected onto the WM/gray interface. FA values were smoothed using $n=50$ iterations of replacement by nearest neighbors. This corresponds to smoothing by approximately 10-mm FWHM on the surface.

(5) Cingulate cortex was divided into rostral and dorsal ACC and posterior cingulate cortex in each hemisphere for each participant by an investigator (GAK) who was blind to group membership. To differentiate between anterior and posterior cingulate cortex we employed an automated surface-based parcellation system (Fischl et al., 2004). The ACC was further divided into dorsal and rostral regions by drawing a line perpendicular to the intercommissural plane at the anterior boundary of the genu of the corpus callosum (Devinsky et al., 1995). FA values of the WM underlying each vertex were averaged for each ROI – dorsal and rostral anterior cingulate cortex (dACC, rACC) and posterior cingulate cortex (PCC) – for each hemisphere and were compared between groups using a repeated measures analysis of variance with group, region, and hemisphere as factors. As a control analysis, the surface areas of the ROIs were compared to determine if there were group differences in the size of the regions sampled. Group differences in hemispheric asymmetry of FA were examined using a difference score that controls for overall differences in FA values: $(LH - RH)/(LH + RH)$, where LH and RH are the FA values in the left and right hemispheres for a particular ROI.

(6) For the vertex-wise analysis, FA maps were registered across participants. This was achieved by registering the T1 surface maps across participants based on gyral folding patterns (Fischl et al., 1999b) and then applying these transformations to the FA maps, which were in register with T1 maps (see steps 3 and 4).

(7) To test for significant group differences in FA in the registered group data, a t -test was performed in the WM underlying each vertex. A false discovery rate (FDR) threshold of $q=0.05$ was applied to control for multiple comparisons (Genovese et al., 2002). For the purposes of calculating the FDR significance threshold, the hypothesis space was restricted to cingulate regions, which were defined in the registered group data using the same anatomical definitions as in the ROI analysis (see step 5). Statistical maps were displayed on a template brain consisting of the averaged cortical surface of an independent sample of 40 adults from the Buckner laboratory at Washington University.

Saccadic regressions

The association between cingulate WM FA values and saccadic latency, adjusting both variables for age, was investigated using multiple regression analyses for each group separately since the

groups differed in variability for both latency and FA. For these regressions FA was the dependent variable and saccadic latency and age were covariates. The mean latency of correct prosaccades or antisaccades was the covariate of interest. Age was regarded as a potential confound given the documented relation of increasing age with decreasing FA (Pfefferbaum et al., 2000; Salat et al., 2005) and longer antisaccade and prosaccade latencies (Munoz et al., 1998). Using age as a covariate, we also examined the relation of FA to antipsychotic dose as indexed by chlorpromazine equivalent (Woods, 2003). The ROI regressions used the mean FA value for each cingulum ROI of each subject. A vertex-wise regression was also performed at each vertex of the cortical surface for the registered group data using a nominal threshold of $p \leq 0.005$ since none of the p -values were significant at FDR $q=0.05$.

Results

Saccadic performance

One control participant was excluded from all analyses involving behavioral data as an outlier since his error rates for antisaccade and prosaccade trials were, respectively, 4.8 and 3.0 standard deviations above the group mean. Schizophrenia participants showed a trend to longer response latencies for both prosaccades ($t(33)=1.82$, $p=0.08$; control: 231 ± 41 ms; schizophrenia: 268 ± 75 ms) and antisaccades ($t(33)=1.82$, $p=0.08$; control: 280 ± 52 ms; schizophrenia: 320 ± 77 ms). Error rates were logit transformed prior to analysis. Patients made more antisaccade errors than controls ($t(33)=2.37$, $p=0.02$; control: $11 \pm 9\%$; schizophrenia: $17 \pm 9\%$), but did not differ in their prosaccade error rate ($t(33)=0.71$, $p=0.48$; control: $4 \pm 3\%$; schizophrenia: $6 \pm 7\%$).

Group differences in FA

ROI analyses

Patients showed reduced FA in cingulate WM compared to controls ($F(1,34)=9.36$, $p=0.004$), and there was a significant group by hemisphere interaction ($F(1,34)=10.20$, $p=0.003$) (Fig. 2). This was due to greater FA reductions in right vs. left cingulate WM in patients. Compared to controls, patients showed significantly decreased FA in right cingulate WM ($F(1,34)=14.57$, $p=0.0005$), and there was a trend to a group by region interaction ($F(1,34)=3.01$, $p=0.06$) indicating larger differences in anterior than posterior cingulate WM regions (rACB: $t(34)=3.42$, $p=0.002$; dACB: $t(34)=3.39$, $p=0.002$; PCB: $t(34)=2.49$, $p=0.02$). In the left hemisphere there was only a trend to reduced cingulate WM FA in patients ($F(1,34)=3.05$, $p=0.09$), no group by region interaction ($F(1,34)=0.86$, $p=0.43$), and only the group difference in rACC WM approached significance (rACC: $t(34)=1.84$, $p=0.08$; dACC: $t(34)=1.42$, $p=0.17$; PCC: $t(34)=0.84$, $p=0.41$). In summary, there was significantly reduced FA in the WM of all three right cingulate ROIs in schizophrenia.

Schizophrenia participants also showed greater asymmetry of cingulate WM FA (left > right) than controls as indexed by difference scores ($F(1,34)=9.74$, $p=0.004$) and although region did not interact with group ($F(1,34)=1.16$, $p=0.32$), patients showed significantly greater leftward asymmetry than controls in dACC WM ($t(34)=3.11$, $p=0.004$), but not in rACC WM ($t(34)=0.51$, $p=0.62$) or PCC WM ($t(34)=1.52$, $p=0.14$). Within the patient group, FA was significantly lower in the right than left hemisphere in dACC WM ($t(16)=4.45$, $p=0.0004$) and PCC WM ($t(16)=3.04$,

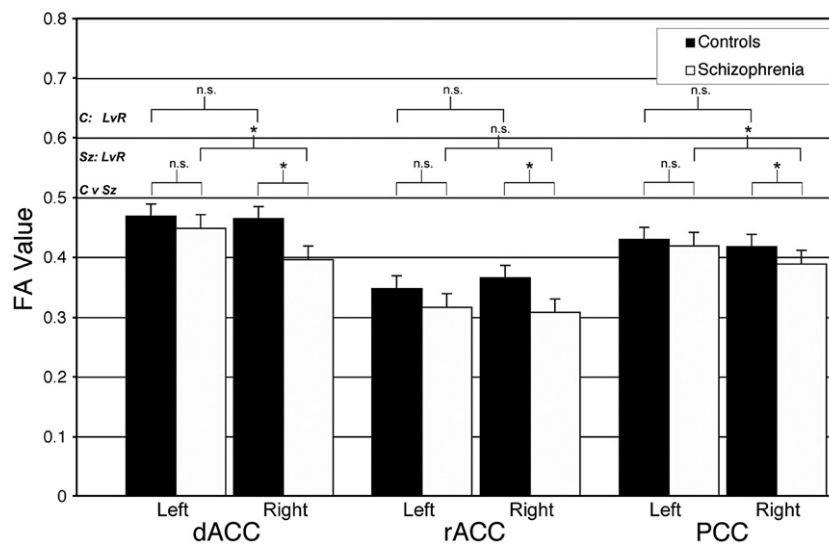


Fig. 2. Bar graphs of mean FA values with standard error bars for each ROI in control and schizophrenia participants. The brackets indicate comparisons between the bars indicated. The left vs. right comparisons within the schizophrenia and control groups are based on difference scores. C=control, L=left hemisphere, R=right hemisphere, Sz=schizophrenia.

$p=0.008$), but not rACC WM ($t(16)=0.96$, $p=0.35$). Control participants did not show significant FA asymmetries in cingulate WM (rACC: $t(18)=-1.65$, $p=0.12$; dACC: $t(18)=0.40$, $p=0.70$; PCC: $t(18)=1.49$, $p=0.15$).

The surface areas of the individual ROIs did not differ between groups ($p>0.35$ for all ROIs).

Vertex-wise analysis

This analysis reproduced the findings of significantly reduced FA in the WM underlying rACC, dACC, and PCC of the right, but not the left hemisphere (Fig. 3). Although it was not included in the hypothesis space for FDR correction, reduced FA was also observed bilaterally in the corpus callosum, consistent with other studies (e.g., Agartz et al., 2001; Ardekani et al., 2003; Foong et al., 2000). Table 2 provides approximate Talairach coordinates for the surface locations of peak differences within the cingulate. (Approximate Talairach coordinates were derived by mapping surface-based coordinates back to the original structural volume for each participant, registering the volumes to the Montreal Neurological Institute (MNI305) atlas (Collins et al., 1994), and averaging the MNI305 coordinates that corresponded to the surface peak across participants. The resulting coordinates were transformed to standard Talairach space using an algorithm developed by Matthew Brett (<http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach>)).

Within-group regressions of FA and saccadic latency

ROI analysis

There were significant relations between reduced FA in the WM of right dACC and rACC and longer latencies for both pro- and antisaccades in schizophrenia (Table 3 and Fig. 4). Controls showed a significant relation between reduced FA in right rACC WM and prosaccade latency. There were no correlations between saccadic latency and FA in the WM of right PCC or in any of the left hemisphere ROIs in either group. A comparison of the coefficients between patients and controls revealed that group differences in the

strength of the relations between latency and FA met or approached significance only in right dACC WM (antisaccades: $z(34)=2.04$, $p=0.04$; prosaccades: $z(34)=1.67$, $p=0.10$). No relations were observed between antipsychotic dose and FA ($p>0.35$ in all ROIs) or saccadic latency ($p>0.25$ for pro- and antisaccades). Adjusting FA and latency values for years of illness instead of age did not substantially change the findings.

Vertex-wise analysis

No significant relations were seen using a FDR threshold that corrected for multiple comparisons. With a nominal threshold of $p\leq.005$ we reproduced the ROI findings of significant relations between reduced FA in right rACC and dACC WM and prolonged latencies of both pro- and antisaccades in schizophrenia (Fig. 4; Table 2 provides approximate Talairach coordinates and exact p -values). The right dACC area showing a relation overlaps with the area of significant FA reduction in schizophrenia. There were also relations in the WM of other regions including the frontal eye field (Paus, 1996) and posterior parietal lobe of the right hemisphere for both pro- and antisaccades. In left dACC WM there was a small area where *greater* FA was associated with longer prosaccade latencies in the schizophrenia group. In controls, saccadic latency was not associated with FA in cingulate WM of either hemisphere or in the WM underlying the frontal eye field or posterior parietal lobe.

Discussion

Relative to controls, patients with schizophrenia showed reduced FA in cingulate WM of the right hemisphere. Moreover, lower FA in the WM underlying anterior cingulate cortex, frontal eye field and posterior parietal cortex of the right hemisphere was associated with longer latencies of volitional saccades. These three densely interconnected regions comprise the key cortical components of a right-hemisphere dominant network for the spatial distribution of attention (Gitelman et al., 1999; Mesulam, 1981, 1990) and also play a critical role in ocular motor control (Pierrot-Deseilligny et al.,

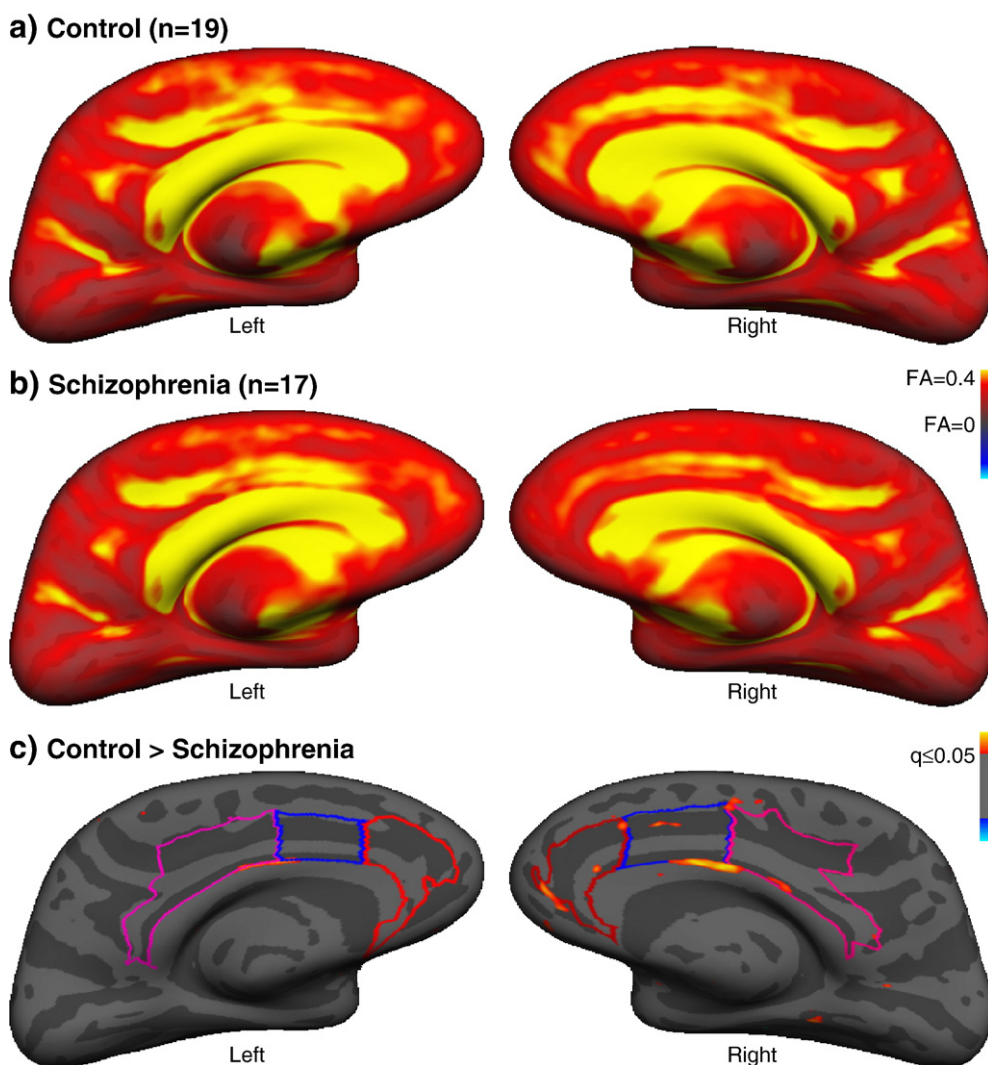


Fig. 3. Vertex-wise group measurements of FA in the registered group data displayed on the inflated medial cortical surface of the template brain. (a) Averaged group FA in healthy participants; (b) averaged group FA in schizophrenia participants; (c) p -value map for group differences in FA at an FDR threshold of $q \leq 0.05$. The rACC is outlined in red; the dACC in blue; and posterior cingulate cortex in magenta.

2004). Thus, the present findings demonstrate that WM microstructural integrity in a network for spatially directed attention and the execution of volitional saccades is associated with saccadic latency in schizophrenia.

The present findings complement a recent report of a relation between increased reaction time on a task measuring selective attention and decreased volume of the right cingulum bundle in schizophrenia (Nestor et al., 2007). More generally, findings of relations between reaction time and FA in other regions support the hypothesis that WM microstructure contributes to individual differences in the speed of cognitive processing (Madden et al., 2004; Tuch et al., 2005). This leads us to hypothesize that reduced integrity of anterior cingulate WM impairs communication in the ocular motor network and by so doing contributes to slower latencies of correct volitional saccades and to inter-individual variability of saccadic latency in schizophrenia.

Frontal eye field, posterior parietal cortex, and dorsal ACC are all thought to contribute to saccadic latency. Pre-target activity in the frontal eye field has been shown to predict the latency of both

prosaccades and antisaccades based on single unit recordings in monkeys (Everling and Munoz, 2000) and functional MRI in humans (Connolly et al., 2005). In humans, damage to frontal eye field, posterior parietal cortex, or to the WM underlying these regions is associated with increased saccadic latency (Pierrot-Deseilligny et al., 1987). Right dorsal ACC lesions have also been found to increase the latencies of pro- and antisaccades (Gaymard et al., 1998).

One may question why, if the same network is implicated in saccadic latency in both patients and controls, was the relation between FA in right dACC WM and saccadic latency stronger in schizophrenia? While this may reflect the greater range of saccadic latency in schizophrenia, a more intriguing possibility is that the abnormally reduced microstructural integrity of right dACC WM in schizophrenia contributes to slower saccadic responses. The observation that the dACC WM region, in which reduced FA is significantly related to longer saccadic latencies, overlaps with the region that shows significant FA reductions in schizophrenia supports this hypothesis (compare Figs. 3c and 4). In controls,

Table 2

Approximate Talairach coordinates corresponding to surface locations of peak group differences and latency–FA correlations in cingulate white matter in the vertex-wise analyses

| | Location | Talairach coordinates | | | <i>p</i> -value |
|---------------------------|------------------|-----------------------|----------|----------|-----------------|
| | | <i>x</i> | <i>y</i> | <i>z</i> | |
| Group FA differences | rACC | 11 | 52 | 5 | 0.00007 |
| | | 6 | 37 | 15 | 0.00009 |
| | dACC | 12 | 13 | 27 | 0.0001 |
| | rACC/dACC border | 12 | 27 | 27 | 0.0002 |
| PS latency–FA correlation | PCC | 3 | –27 | 11 | 0.0003 |
| | rACC | 11 | 51 | 18 | 0.0001 |
| | dACC | 12 | 9 | 30 | 0.00007 |
| AS latency–FA correlation | rACC/dACC border | 12 | 26 | 25 | 0.0003 |
| | rACC | 11 | 51 | 18 | 0.00001 |
| | dACC | 12 | 9 | 30 | 0.0003 |
| | rACC/dACC border | 12 | 26 | 25 | 0.0004 |

PS=prosaccades, AS=antisaccades, rACC=rostral anterior cingulate white matter, dACC=dorsal anterior cingulate white matter, PCC=posterior cingulate white matter.

dACC WM integrity may be adequate for saccades, and if this were the case, variability in WM microstructure would play a less significant role in determining saccadic latency.

Neuroimaging, electrophysiological, and lesion studies have implicated the dorsal ACC in volitional saccades, but we also, unexpectedly, found a relation of saccadic latency to FA in the WM underlying right rostral ACC in both patients and controls. We recently reported differential activity in the rostral ACC for error vs. correct antisaccades in healthy participants (Polli et al., 2005a). The timing of activation suggested that rACC contributed both to response preparation and evaluation, an interpretation that is consistent with previous findings (e.g., Drevets and Raichle, 1998; van Veen and Carter, 2002). The role of the rACC in performance optimization may account for the relation of greater integrity of rACC WM to faster saccadic responses.

In the present study, saccadic latencies were associated with lower FA primarily in the right hemisphere. In humans, the right hemisphere is thought to play a dominant role in directing both spatial attention (Heilman and Valenstein, 1979; Mesulam, 1981) and eye gaze (De Renzi et al., 1982; Meador et al., 1989). We interpret the asymmetric relations we observed as being compatible with evidence of right-hemisphere specialization for spatial attention and volitional ocular motor control.

Moreover, relative to controls, patients showed significantly reduced FA in cingulate WM of the right hemisphere only, and significantly greater left>right asymmetry of FA in dACC WM. Within the patient group, FA in WM underlying dACC and PCC was significantly lower in the right than the left hemisphere. Controls did not show any significant asymmetries of FA in cingulate WM. Previous studies have reported either right (Hao et al., 2006) or bilateral (Ardekani et al., 2003; Kubicki et al., 2003; Wang et al., 2004) cingulum bundle FA reductions in schizophrenia, and left>right asymmetry of FA in the cingulum bundle in healthy participants (Gong et al., 2005) and in both schizophrenia patients and controls (Kubicki et al., 2003; Park et al., 2004b; Wang et al., 2004). In two of three studies, asymmetry, though present, was reduced in schizophrenia (Park et al., 2004b; Wang et al., 2004). This differs from our finding of significant asymmetry only in schizophrenia, which was not predicted and therefore warrants replication. We interpret our findings of abnormally asymmetrical and reduced FA in right dACC WM in schizophrenia, and the relation of this reduction to longer saccadic latencies, to suggest a pathological process affecting WM rather than normal developmental causes of asymmetry that are associated with functional lateralization.

Several potential limitations of the present study are considered below. First, it is important to emphasize that FA is an indirect measure of WM microstructure and because its biophysical mechanisms are not completely understood, it is not possible to attribute the relations we observed to a particular WM property. WM density and volume may have contributed to group differences in FA and its relations with saccadic latency, a possibility that requires further study.

Second, group differences in general cognitive ability may contribute to our findings. In this and many other studies of schizophrenia, participants are matched for parental socioeconomic status rather than participant socioeconomic status or IQ. The primary rationale for this strategy is that reduced IQ in schizophrenia, which predates the onset of illness and then further declines (Seidman et al., 2006), may reflect cognitive deficits that are core to schizophrenic pathology, and not an artifact that should be controlled (Meehl, 1970). Obtaining valid estimates of premorbid IQ in schizophrenia is also problematic since amotivation, psychosis, and related disruptions of attention may prevent optimal engagement in cognitive testing. Tests that are relatively robust to these effects, such as single word reading and spelling (Dalby and Williams, 1986), are sensitive to educational attainment, which may also be compromised by schizophrenia and its prodrome. A relationship between WM physiology and IQ has been theorized

Table 3

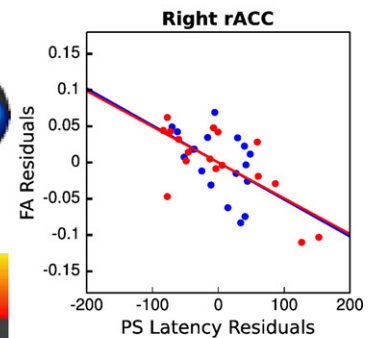
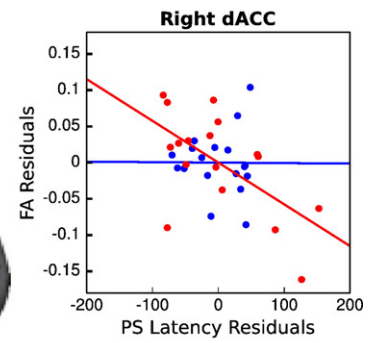
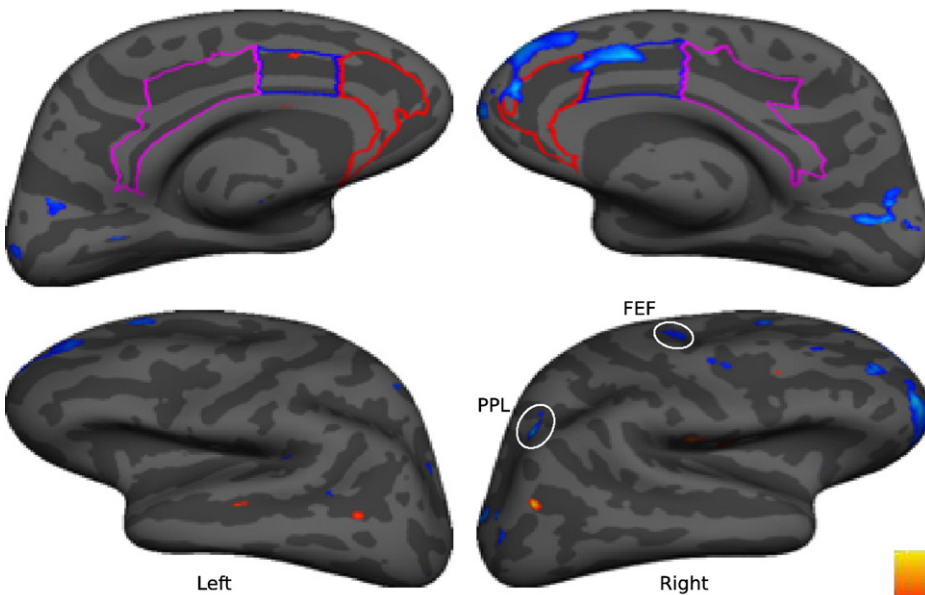
Change in FA due to a 1s change in latency, from a regression model that adjusts both FA and latency for the effect of age

| | | | Right | | | Left | | |
|----------------------------------|----|----------|------------|-------------|------------|------------|------------|------------|
| | | | rACC | dACC | PCC | rACC | dACC | PCC |
| Controls (<i>n</i> =18) | PS | Estimate | –0.51±0.24 | –0.007±0.28 | –0.09±0.19 | –0.08±0.30 | –0.34±0.20 | –0.09±0.26 |
| | | <i>p</i> | 0.05 * | 0.98 | 0.64 | 0.81 | 0.11 | 0.73 |
| | AS | Estimate | –0.28±0.20 | 0.05±0.22 | –0.07±0.15 | 0.05±0.24 | –0.20±0.17 | 0.10±0.21 |
| | | <i>p</i> | 0.18 | 0.81 | 0.65 | 0.84 | 0.24 | 0.64 |
| Schizophrenia (<i>n</i> =17) | PS | Estimate | –0.49±0.12 | –0.58±0.20 | –0.12±0.13 | –0.23±0.17 | –0.11±0.17 | –0.15±0.12 |
| | | <i>p</i> | 0.001 * | 0.01 * | 0.34 | 0.20 | 0.53 | 0.25 |
| | AS | Estimate | –0.50±0.12 | –0.56±0.20 | –0.14±0.12 | –0.21±0.17 | –0.16±0.17 | –0.16±0.12 |
| | | <i>p</i> | 0.001 * | 0.02 * | 0.27 | 0.23 | 0.35 | 0.21 |

The results are presented as changes, corresponding standard errors, and *p*-values.

* Indicates a significant relation.

a) Prosaccade



b) Antisaccade

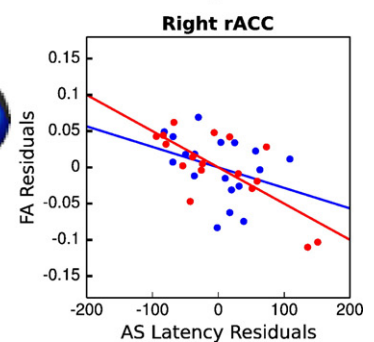
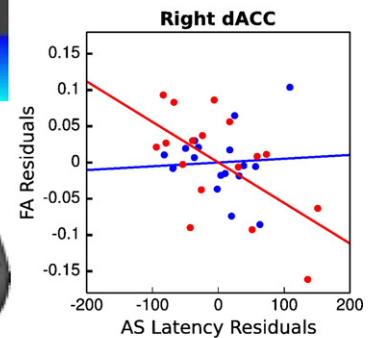
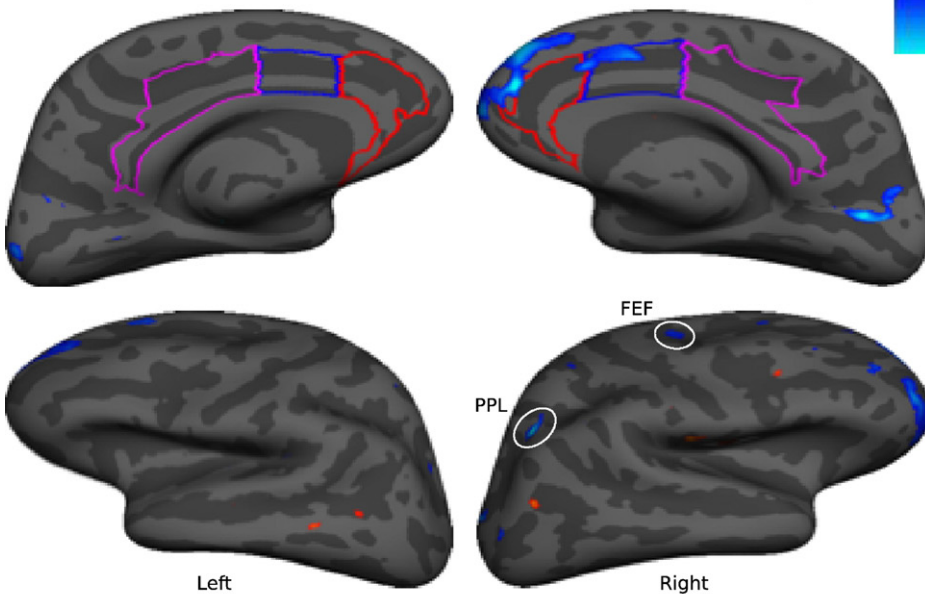


Fig. 4. Regression analyses of FA with latency using age as a covariate in schizophrenia. The left and middle columns display the results of the vertex-wise regression on the inflated medial and lateral cortical surfaces for (a) prosaccades and (b) antisaccades. The rACC is outlined in red; the dACC in blue; and posterior cingulate cortex in magenta. Regions of significant correlation in the WM underlying the frontal eye field (FEF) and posterior parietal lobe (PPL) of the right hemisphere are indicated by white circles. The right column displays the results of the ROI regressions for dACC and rACC WM as partial regression added variable plots (Atkinson, 1985) of the effect on FA of a 1 ms change in (a) prosaccade latency and (b) antisaccade latency, after having adjusted both FA and latency for age. The x -axis values are the residuals of latency on age, and the y -axis values are the residuals of FA on age. The values and least squares lines for schizophrenia participants are red, and controls are blue.

based of the role of increased myelination in promoting faster and more efficient neural communication (Luciano et al., 2004). This theory is supported by findings in healthy children of direct relations between IQ and FA in the WM of frontal and parieto-occipital association areas bilaterally (Schmithorst et al., 2005).

The present study investigated a specific deficit, slowing of volitional saccades, and its relation to WM physiology in a region that contributes to saccadic latency—dACC (Gaymard et al., 1998). While it is possible that a group difference in general cognitive ability contributed to FA differences and their relation to behavior,

if it were the primary factor, one would expect to see widespread changes and correlations, rather than the fairly circumscribed ones that we observed.

Third, this study may have suffered from a lack of power due to the relatively small sample size, particularly with regard to group differences in saccadic latency and its associations with FA. While our primary (ROI) analysis showed the predicted significant relations between FA in dACC WM and saccadic latency in patients, in the vertex-wise analysis the significance of these relations did not pass correction for multiple comparisons. In addition, unlike our previous study of this task, group differences in saccadic latency approached, but did not meet, statistical significance (Manoach et al., 2002). Other groups have also reported longer latencies for correct prosaccades and/or antisaccades (e.g., Fukushima et al., 1994; Harris et al., 2006; Hutton et al., 1998) but these findings are not consistent (e.g., Clementz et al., 1994). These inconsistencies likely stem from variations in task design that determine which cognitive processes are required, but also reflect differences in statistical power. This is illustrated by a recent multi-site study of antisaccades that showed significantly increased latency of correct antisaccades in schizophrenia ($n=143$ patients, 195 controls, $p<0.0001$) (Radant et al., 2007). The magnitude of the group difference for antisaccade latency was comparable to that of the present study (37 and 40 ms respectively). Although latencies for patients were longer at all seven sites, the difference reached statistical significance only at one site. (The probability of all seven sites having the same direction of group difference by chance is 0.016). Along with the present data, this suggests that correct volitional saccades have longer latencies in schizophrenia, but that larger samples are required to reliably demonstrate this effect due to its size and to measurement variability in schizophrenia.

Finally, in the present study, the schizophrenia sample was limited to chronic, medicated patients. Antipsychotic dose was not related to saccadic latency or to FA in the cingulum ROIs. While it would be difficult to account for the findings on the basis of medications, particularly with regard to their lateralization, the effects of antipsychotic medications on WM microstructure are unknown and cannot be ruled out as a factor in the current findings. It is also possible that reduced WM microstructure might be related to the progression of schizophrenia and would not be seen in patients early in the course of illness.

In summary, this study documented FA reductions in the WM underlying cingulate cortex in chronic, medicated schizophrenia and related these abnormalities to saccadic latency. These findings demonstrate an association between deficits in volitional ocular motor control and reduced microstructural integrity of the WM underlying key cortical components of a network for saccadic execution. They suggest that ACC WM abnormalities contribute to slower performance of volitional saccades and to inter-individual variability of saccadic latency in schizophrenia.

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