# Altered Interhemispheric and Temporal Lobe White Matter Microstructural Organization in Severe Chronic Schizophrenia

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Diffusion MRI investigations in schizophrenia provide evidence of abnormal white matter (WM) microstructural organization as indicated by reduced fractional anisotropy (FA) primarily in interhemispheric, left frontal and temporal WM. Using tract-based spatial statistics (TBSS), we examined diffusion parameters in a sample of patients with severe chronic schizophrenia. Diffusion MRI data were acquired on 19 patients with chronic severe schizophrenia and 19 age- and gender-matched healthy controls using a 64 gradient direction sequence, ($b = 1300 \, s/mm^2$) collected on a Siemens 1.5T MRI scanner. Diagnosis of schizophrenia was determined by Diagnostic and Statistical Manual for Mental Disorders 4th Edition (DSM-IV) Structured Clinical Interview for DSM disorder (SCID). Patients were treatment resistance, having failed to respond to at least two antipsychotic medications, and had prolonged periods of moderate to severe positive or negative symptoms. Analysis of diffusion parameters was carried out using TBSS. Individuals with chronic severe schizophrenia had significantly reduced FA with corresponding increased radial diffusivity in the genu, body, and splenium of the corpus callosum, the right posterior limb of the internal capsule, right external capsule, and the right temporal inferior longitudinal fasciculus. There were no voxels of significantly increased FA in patients compared with controls. A decrease in splenium FA was shown to be related to a longer illness duration. We detected widespread abnormal diffusivity properties in the callosal and temporal lobe WM regions in individuals with severe chronic schizophrenia who have not previously been exposed to clozapine. These deficits can be driven by a number of factors that are indistinguishable using *in vivo* diffusion-weighted imaging, but may be related to reduced axonal number or packing density, abnormal glial cell arrangement or function, and reduced myelin.

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## INTRODUCTION

Schizophrenia is a chronic and disabling mental disorder (Jablensky, 2000) associated with gray matter (GM) and white matter (WM) abnormalities. Recent meta-analyses of voxel-based imaging studies showed widespread clusters of GM volume reductions with no regions of volume increases, and widespread WM deficity in schizophrenia (Bora *et al*, 2011). Abnormalities in WM detected using diffusion MRI may indicate alterations in commissural and association fibers connecting GM regions (Ellison-Wright and Bullmore, 2009), Moreover, progressively more severe deficits in WM anisotropy have been found in cross-sectional studies comparing first episode and chronic patients (Friedman *et al*, 2008; Kong *et al*, 2011).

Standard structural MRI lacks orientational contrast making it impossible to distinguish between different WM tracts. Diffusion-weighted MRI or DWI, however, allows us to indirectly probe the microstructural organization of WM (Le Bihan *et al*, 2001), while providing orientational information to visualize and differentiate between large fiber bundles. DWI techniques measure the diffusion rate of water molecules moving within and between axonal bundles. Diffusion is larger in the directions parallel to the axon bundle, than in the plane perpendicular to these

axons. Measuring diffusion in multiple directions with diffusion tensor imaging (DTI) therefore allows us to infer differences in the microstructural organization or orientation of WM bundles between groups of subjects (Basser et al, 1994). Fractional anisotropy (FA), an outcome parameter of DTI, is determined by a combination of factors including fiber orientation, axonal packing density, membrane permeability, and to a lesser extent the degree of myelination (Beaulieu, 2002; Le Bihan et al, 2001; Pierpaoli et al, 1996; Tournier et al, 2011). DTI outcome parameters also include axial diffusivity (AD) (diffusion in the principal direction of an axon bundle) and radial diffusivity (RD) (diffusion perpendicular to the direction of an axon bundle). AD has been shown to be modulated by axonal degeneration, whereas RD is more specifically related to changes in the myelin sheath (Song et al, 2002).

In schizophrenia, diffusion MRI studies have shown significant decrease in FA in multiple WM fiber bundles relative to healthy controls using whole brain (Mori et al, 2007b; Rotarska-Jagiela et al, 2009; Schlosser et al, 2007; Shergill et al, 2007; Sussmann et al, 2009), restricted voxel-based (Douaud et al, 2007; Karlsgodt et al, 2008; Lim et al, 1999) and reconstructed tract-based (McIntosh et al, 2008; Phillips et al, 2009; Whitford et al, 2010) analysis methods. Longitudinal studies highlight the progressive nature of these deficits. In WM, a single study of individuals experiencing their first psychotic episode did not detect microstructural changes (as assessed by DTI) in the corpus callosum relative to healthy controls (Price et al, 2005). Studies including both first episode and chronic patients showed that patients with chronic disease had significantly reduced FA compared with controls, reaching only a trend level in first episode patients (Friedman et al, 2008; Kong et al, 2011). This implies a progressive nature associated with illness duration in schizophrenia, as previously reported in a structural study investigating GM and WM volumes reporting a progressive reduction in the frontal WM volume in patients (Ho et al, 2003).

The most consistently implicated WM bundles in chronic schizophrenia samples include the genu of the corpus callosum (Kong et al, 2011; Kubicki et al, 2008; Rotarska-Jagiela et al, 2008; Whitford et al, 2010), the splenium of the corpus callosum (Agartz et al, 2001; Foong et al, 2000), anterior cingulate (Camchong et al, 2011; Sun et al, 2003; Wang et al, 2004), and anterior limb of the internal capsule (ALIC) (Buchsbaum et al, 1998; Sussmann et al, 2009). However, none of these studies were specifically carried out on a treatment-resistant clozapine-naive group, and clozapine has previously been reported to cause structural changes in the brain (Ho et al, 2003; Molina et al, 2005; Scheepers et al, 2001).

However, other studies contradict FA reductions in schizophrenia and report no significant FA difference in the genu but only in the splenium (Agartz et al, 2001; Foong et al, 2000), and no FA difference in any WM region (Foong et al, 2002; Kito et al, 2009; Levitt et al, 2010; Wang et al, 2003). Discrepancies in these findings could be attributed to methodological differences, subjective rater-based variation between studies such as region of interest (ROI) placement, and clinical heterogeneity including stage of illness and medication exposure. The contribution of long-term exposure to antipsychotic medication, further psychotic

episodes, and illness contribute to these differences is unclear and difficult to examine explicitly.

In the present study, we examine changes in WM FA, radial and AD in a relatively clinically homogenous group of treatment-resistant individuals with severe chronic schizophrenia.

## MATERIALS AND METHODS

### Participants

DTI data were acquired from 19 individuals with severe chronic schizophrenia and 19 gender- and aged-matched healthy controls (Table 1). Patients were recruited from the in- and out-patient units in the University College Hospital Galway (UCHG) and in the catchment area of HSE West of Ireland.

All patients were diagnosed by experienced psychiatrists, using the Structured Clinical Interview for DSM disorders (SCID) (First et al, 2002b), as meeting the criteria for schizophrenia per the Diagnostic and Statistical Manual for Mental Disorders 4th Edition text revision (DSM-IV-TR) (Association AP, 2000). In order to provide information about symptom severity and functioning, the Positive and Negative Symptom Scale (PANSS) (Kay et al, 1987) and Global Assessment of Functioning Score (GAF) (Hall, 1995) were administered for each patient. All patients with severe chronic schizophrenia were treatment resistant at the time of scanning and were being considered for treatment with clozapine, an atypical antipsychotic medication licensed for treatment resistance. Treatment resistance was defined as the failure to respond to at least two antipsychotic medications, one of which an atypical, with a prolonged period of moderate to severe positive and/or negative symptoms (mean duration of illness = 14.42 years + 8.16, range = 4–39 years). At the time of scanning, all patients were medicated with atypical antipsychotics (olanzapine $n = 10$, aripiprazole $n = 4$, paliperidone $n = 2$, quetiapine $n = 2$, and amisulpiride $n = 1$), with some on two or more medications (atypical $n = 10$, atypical + SSRI $n = 4$, atypical + TCA $n = 1$, and atypical + IM typical every 2 weeks $n = 4$). No patients had commenced clozapine at the time of scanning.

The control group consisted of 19 participants with no current or past axis I or II disorders (DSM-IV-TR) and were screened using the SCID-Non-Patient Version (First et al, 2002a) and matched to the patients for age and gender.

**Table 1** Demographic Characteristics of Controls and Patients

|  | HC | SZ | Group difference |
|---|---|---|---|
| Number | 19 | 19 | — |
| Gender (M/F) | 14, 5 | 14, 5 | — |
| Age (years) (range) | 38.21 (10.29) (23–57) | 38.10 (9.55) (24–59) | t(36) = 0.095, p = 0.974 |
| Duration of illness (years) (range) | — | 14.42, 8.16 (4–39) |  |
| PANSS total (range) | — | 52.31, 17.46 (17–89) |  |

Abbreviations: HC, healthy controls; SZ, patients with chronic schizophrenia; PANSS, Positive and Negative Symptom Scale (PANSS based on a 0–6 scales).

Controls were excluded if there was a personal or family history of a psychiatric illness.

In addition, all participants were subject to the following exclusion criteria: neurological disorders, learning disability, comorbid substance or alcohol misuse, a history of a head injury resulting in loss of consciousness $>5$ min, and general MRI contraindications including pregnancy. Ethical approval was granted by both the University College Hospital Galway and the National University of Ireland Galway Ethics committees, and written informed consent was obtained from each participant.

## Image Acquisition

DTI data were acquired on a 1.5T Siemens Magnetom Symphony MRI scanner (Erlangen, Germany), utilizing an Echo Planar Imaging (EPI) based diffusion sequence acquired using parallel imaging (GRAPPA, factor 2), 64 independent diffusion gradient directions, $b = 1300$ s/mm$^2$, with 7 reference non-diffusion-weighted images ($b$-value $= 0$ s/mm$^2$), TR $= 8100$ ms, TE $= 95$ ms, in-plane voxel size of $2.5 \times 2.5$ mm, and a slice thickness of 2.5 mm, and SNR of $b = 1000$ s/mm$^2$ images $>20$. After scout images, the total imaging time was 10.24 min for the diffusion MRI sequence. Diffusion parameters were based on the study by Jones et al (1999), outlining the optimal strategies for measuring diffusion in anisotropic systems by MRI .

## Image Processing and Statistics

ExploreDTI (Leemans A JB and Jones, 2009) was used to process the diffusion MRI data and consisted of the following steps: (i) correction for motion and eddy current induced geometric distortions with rotation of the b-matrix to ensure the orientation information is correctly preserved (Leemans and Jones, 2009); (ii) estimation of the diffusion tensor using a robust nonlinear regression method (Chang et al, 2005); and (iii) calculation of FA, AD, and RD maps. Subsequently, voxel-based statistical analysis was carried out using the tract-based spatial statistics (TBSS) approach (Smith et al, 2006) as follows: FA images were nonlinearly registered using FNIRT (Anderson et al, 2007) to the MNI152 standard space, resulting in a standard space version of each individual FA image. Next, a study-specific thinned mean FA skeleton (threshold of 0.2 to exclude voxels of GM, CSF, and WM voxels with a low FA, which is associated with less certainty) was generated to represent the centre of all WM FA voxels common to the group. Alignment of each individuals FA image to the skeleton is carried out by searching a given subject's FA image in the (already-computed) perpendicular tract direction to find the maximum FA value and assign this value to the skeleton voxel. Voxel-wise statistics is then carried out using Randomise, a permutation-based nonparametric analysis program (Nichols and Holmes, 2002). Qualitative analysis was carried out at each step of TBSS in order to check image quality of original data, determining the correct FA threshold, and alignment of each individuals FA image to the mean FA skeleton. All analyses included age as a covariate to increase the sensitivity of the analysis and to detect real differences between the groups, as age has been shown to effect FA (Bendlin et al, 2010). Multiple comparison

correction was applied using threshold-free cluster enhancement (TFCE) (Smith and Nichols, 2009) with a reporting cutoff of $p < 0.05$ applied. TFCE enhances cluster-like structures in an image and negates the need for defining an initial cluster-forming threshold; no spatial smoothing is required.

The original FA nonlinear registration was applied to AD and RD maps, which were then projected onto the mean FA skeleton. Randomise voxel-based statistical analysis was carried out as above, incorporating TFCE correction for multiple comparisons, to test for a main effect on AD and RD.

In order to further investigate what was driving intergroup differences, mean FA was extracted from the clusters where the highest statistical group difference was identified using a $p$-value cutoff threshold of $p < 0.05$; the anatomical regions to which these belonged were determined using the JHU white-matter tractography atlas (Mori and van Zijl, 2007a). These were compared with illness severity (PANSS) and illness duration using a partial correlation controlling for age. Statistical analyses were carried out using PASW Statistics 18 (© 2010, SPSS Inc.).

## RESULTS

The demographic characteristics of the participants are given in Table 1. Voxels showing significantly reduced FA were identified using the tractography atlas (Mori and van Zijl, 2007a). FA was lower in the schizophrenic group relative to healthy controls (Figure 1) in the genu, body, and splenium of the corpus callosum, bilaterally in the temporal portions of the ILF, superior longitudinal fasciculus (SLF), external capsule, temporal uncinate fasciculus (UF), posterior limb of the internal capsule, the left ALIC, fornix, cerebellar peduncles, and the corticospinal tract at the level of the brainstem. There were no voxels of increased FA in patients compared with controls.

RD was significantly higher in the patient group compared with controls (Figure 2). Voxels of significantly higher RD were located in the genu, body, and splenium of the corpus callosum, the right ILF, posterior limb of the internal capsule, and the external capsule. There were no voxels of increased RD in the control group vs chronic schizophrenia group. AD was not significantly different between the diagnostic groups.

Mean FA was extracted from the clusters where the highest statistical group difference was identified using a $p$-value cutoff threshold of $p < 0.05$. This included the genu (1309 mm$^3$, $T = 0.79$–3.9, median $= 1.78$), body (2069 mm$^3$, $T = 0.79$–5.2, median $= 1.87$), and splenium (723 mm$^3$, $T = 0.70$–3.8, median $= 1.50$) of the corpus callosum (Figure 3a). Illness duration was negatively related to FA in the splenium (cc $= -0.561$, $p = 0.015$) (Figure 3b) but not in the genu (cc $= -0.412$, $p = 0.089$) or body (cc $= -0.288$, $p = 0.247$) of the corpus callosum in the schizophrenia group; however, this did not survive the Bonferroni correction for multiple comparisons. FA in these callosal regions did not relate significantly to illness severity (PANSS score $n = 19$, range $= 17$–89, mean $= 52.31$, SD $= 17.46$, genu cc $= 0.206$ $p = 0.41$, body cc $= 0.304$ $p = 0.220$, and splenium cc $= -0.022$ $p = 0.932$). There was no correlation between
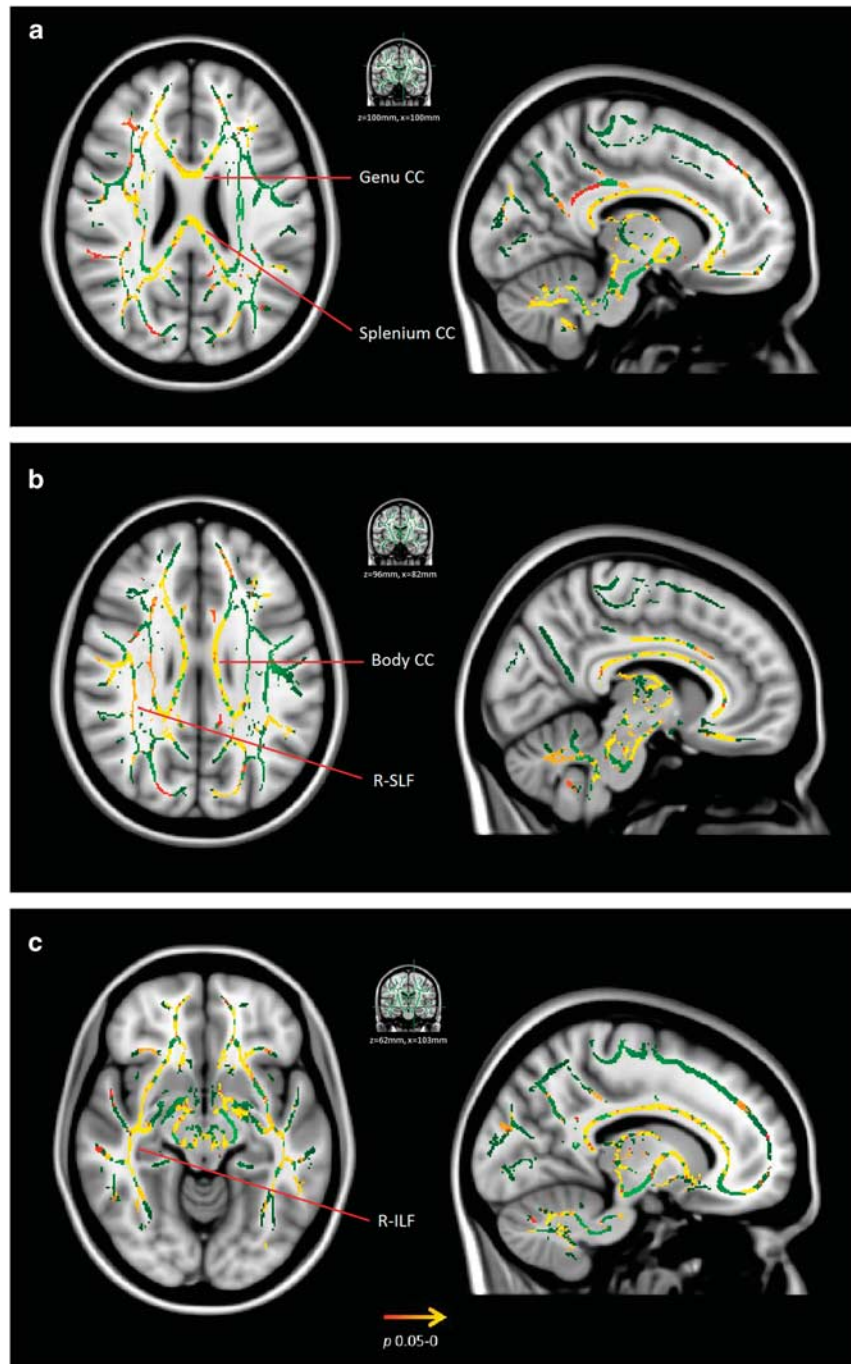
**Figure 1** Regions of reduced fractional anisotropy (FA) in the schizophrenia relative to the control group. Clusters of voxels ($p < 0.05$, threshold-free cluster enhancement, TFCE) with significantly reduced FA in chronic schizophrenia compared with controls in (a) the genu, body, and splenium of the corpus callosum, (b) the body of the corpus callosum and the superior longitudinal fasciculus (SLF) (more prominent on the right), and (c) in the ILF. Significant clusters ($p < 0.05$, TFCE) are denoted in a red ($p = 0.05$) to yellow (lowest $p$-value) color intensity scale given at the bottom of the figure and in radiological format.

patient FA and chlorpromazine equivalents for each patient's medication status at the time of scanning.

## DISCUSSION

We detected interhemispheric, cortico-cortical association, brainstem, and brainstem level projection fiber decreases in FA (Figure 1), which may reflect deficits in the microstructural organization of WM in a group of clozapine-naive individuals with severe chronic schizophrenia. The FA reductions extended throughout the corpus callosum, and were present bilaterally in parietal portions of the SLF, temporal ILF and UF, the posterior limb of the internal capsule, and the external capsule. They were also evident in the left ALIC, the fornix, the posterior projections of the middle cerebellar peduncle, midline portions of the superior and inferior cerebellar peduncles,
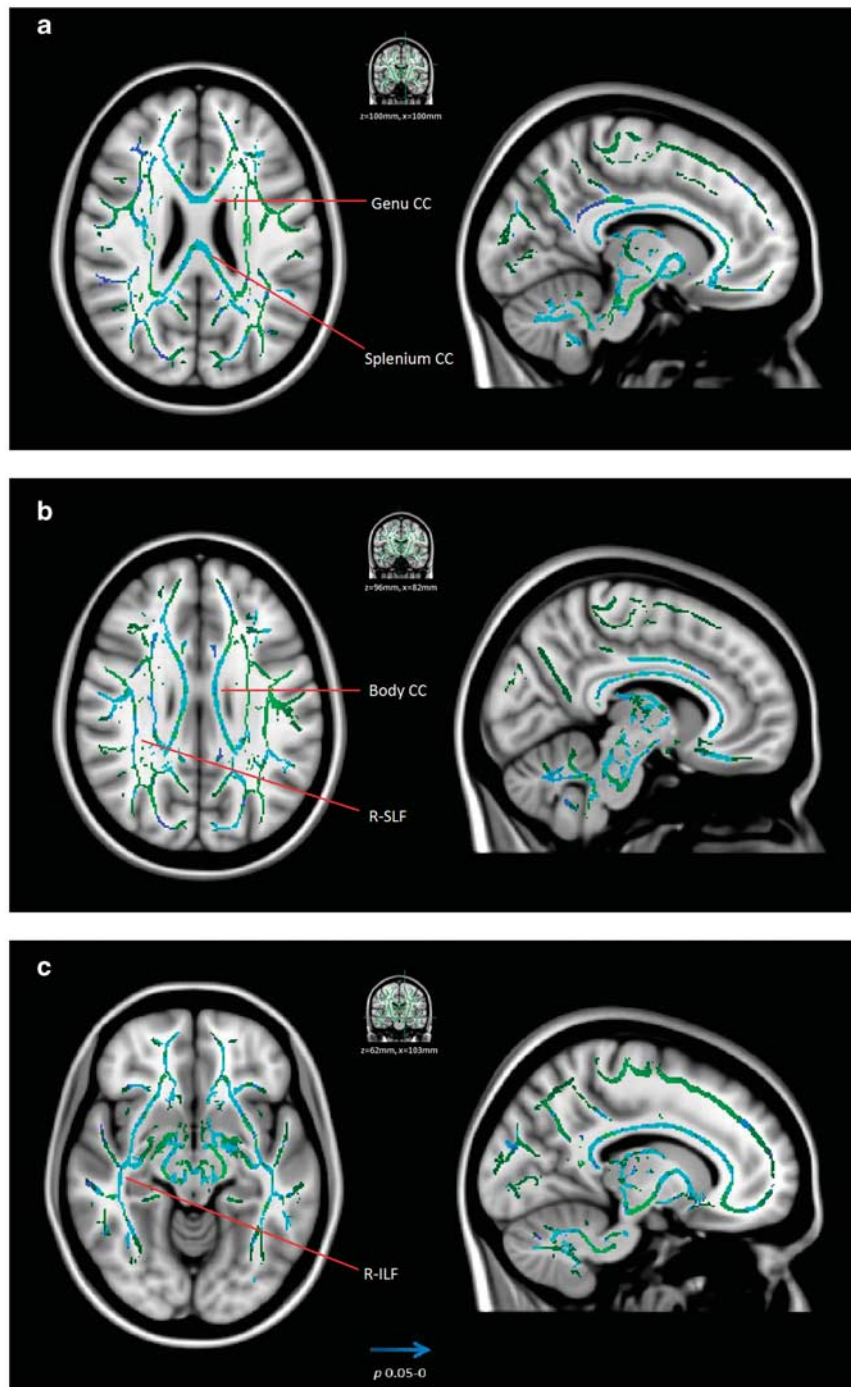
**Figure 2** Regions where radial diffusivity (RD) was higher in the schizophrenia than the control group in the (a) genu and splenium of corpus callosum, (b) body of the corpus callosum and R-SLF, and (c) in the R-ILF. Increased RD in the chronic schizophrenia compared with the control group were evident in the genu ($726\,mm^3$, $T = 0.31$–3.64, median = 1.78), body ($1421\,mm^3$, $T = 0.38$–3.98, median = 1.87), and splenium ($723\,mm^3$, $T = 0.23$–4.22, median = 2.06) of the corpus callosum ($p < 0.05$, threshold-free cluster enhancement, TFCE). Significant clusters ($p < 0.05$, TFCE) are denoted in a blue ($p = 0.05$) to light blue (lowest $p$-value) color intensity scale given at the bottom of the figure and in radiological format.

and in the brainstem level of the corticospinal tracts. For a subgroup of these regions, this deficit was accompanied by increased RD: the corpus callosum, temporal portions of the right ILF including a region overlapping the right UF, the right external capsule, and the right posterior limb of the internal capsule (Figure 2). There were no group differences in AD and no regions of greater FA or reduced RD in the schizophrenia group relative to controls. The changes detected in FA and RD in schizophrenia may reflect deficits in microstructural organization such as alterations to the cellular membrane, fiber density, and the myelin sheath, and may be negatively related to the duration of illness, as reported here in the splenium of the corpus callosum.
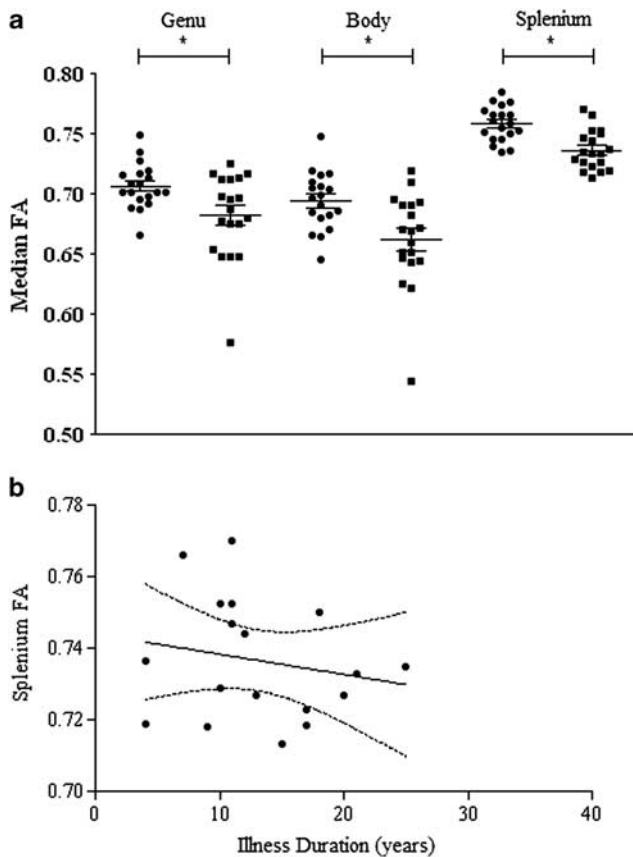
**Figure 3** (a) Median fractional anisotropy (FA) is reduced in three regions of the corpus callosum in the schizophrenia (squares) compared with control subjects (circle). (b) Correlation of the splenium FA and illness duration in chronic schizophrenia. (a) Reduced FA in the genu (1309 mm$^3$, $T = 0.79–3.9$, median = 1.78), body (2069 mm$^3$, $T = 0.79–5.2$, median = 1.87), and splenium (723 mm$^3$, $T = 0.70–3.8$, median = 1.50) of the corpus callosum in the schizophrenia (squares) compared with control subjects (circle). (b) Correlation of the splenium FA and illness duration in chronic schizophrenia.

The degree of anisotropic diffusion in WM is most directly influenced by the relative arrangement and orientation of the fibers. Thus, reduced FA (or more precisely in this case, the increase in RD detected) implicates several possible factors including reduced axonal number or packing density and cellular membrane abnormalities that lead to increased permeability such as loss of myelin or inconsistent fiber orientation (Beaulieu, 2002). Other factors that may affect the estimation of the diffusion tensor metrics include partial volume averaging and the existence of 'crossing fibers' configurations (Alexander et al, 2001; Jeurissen et al, 2012; Vos et al, 2012; Vos et al, 2011; Wheeler-Kingshott and Cercignani, 2009).

The observed differences in diffusivity measures were most prominent across the corpus callosum and highest in the body (4.6% median $T = 1.9$, range 0.79–5.2, Cohen's d = 0.98), the genu (3.5% median $T = 1.8$, range 0.79–3.9, Cohen's d = 0.86), and the splenium (2.9% median T = 1.52, Cohen's $d = 1.41$). The latter is consistent with the pathophysiology of the corpus callosum in schizophrenia as evidenced by previous in vivo diffusion (Bora et al, 2011; Foong et al, 2000; Kong et al, 2011; Kubicki et al, 2008; Patel

et al, 2011). Postmortem studies have shown a gender-diagnosis effect of reduced axonal number (Highley et al, 1999a), oligodendrocyte density loss (Hof et al, 2003), and lower levels of immunoreactivity of oligodendrocyte-associated proteins in the genu of the corpus callosum (Flynn et al, 2003). Diffusion-weighted imaging has been relatively consistent in reporting reduced callosal FA in chronic schizophrenia (Douaud et al, 2007; Koch et al, 2010; Kubicki et al, 2008; Miyata et al, 2010; Mori et al, 2007b; Rotarska-Jagiela et al, 2008), including during remission (Koch et al, 2010) and less consistently in studies examining individuals at the first episode (Cheung et al, 2008; Gasparotti et al, 2009; Perez-Iglesias et al, 2010b; Peters et al, 2008; Price et al, 2005; Szeszko et al, 2005) or in earlier stages of illness (Davenport et al, 2010; Douaud et al, 2007; Kyriakopoulos and Frangou, 2009). Directly comparing first episode and chronic groups supports more severe changes in FA in the genu of the corpus callosum (Friedman et al, 2008; Kong et al, 2011), the left ILF (Friedman et al, 2008), and ALIC (Bora et al, 2011) in the chronic group including relative to the first episode group. By contrast, the large scale meta-analysis by Bora et al (2011) has reported the opposite, specifically for the genu of the corpus callosum, with FA being lower in the first episode relative to the chronic group with schizophrenia.

Four meta-analyses have been conducted on diffusion imaging findings in cross-sectional studies (Bora et al, 2011; Di et al, 2009; Ellison-Wright and Bullmore, 2009; Patel et al, 2011). The two earlier studies (Di et al, 2009; Ellison-Wright and Bullmore, 2009) performed meta-analyses of studies that used a voxel-based studies and detected deficits in the genu and splenium in one case (Ellison-Wright and Bullmore, 2009) but not in the other (Di et al, 2009). A recent study conducted two meta-analyses (Patel et al, 2011) to examine the genu and splenium of the corpus callosum in 213 controls and 202 patients and reported reduced FA in both regions that were significant in the splenium (effect size 0.53) but subthreshold for reduced FA for the genu (effect size 0.22). However, this study included only those studies ($n = 7$) using a ROI approach. The fourth meta-analysis included 699 individuals with schizophrenia and 681 controls across 24 studies that used a voxel-based analysis approach and detected significant deficits in FA. Widespread deficits were detected, including interhemispheric fibers, specifically in the bilateral genu of the corpus callosum as well as medial frontal WM, the right ALIC, the right external capsule, and temporal lobe WM (Bora et al, 2011). Thus, it is plausible that the small effect size reported by Patel et al (2011) is due to the restriction of the meta-analysis to just seven studies. Not accounted for in these analyses are the few negative studies that exist. Two previous studies reported no differences in FA throughout the brain (Foong et al, 2002; Murakami et al, 2011); others have reported widespread lower FA but did not detect significant differences in the genu of the corpus callosum specifically (Agartz et al, 2001; Foong et al, 2000; Karlsgodt et al, 2008; Kubicki et al, 2008; Seal et al, 2008).

Several additional regions beyond the callosal body have been implicated in chronic schizophrenia including SLF (Rotarska-Jagiela et al, 2009; Rowland et al, 2009; Seok et al, 2007; Shergill et al, 2007; Szeszko et al, 2008), ILF (Ashtari et al, 2007; Lee et al, 2009; Phillips et al, 2009; Rotarska-

Jagiela et al, 2009; Seal et al, 2008), UF (Burns et al, 2003; McIntosh et al, 2008; Miyata et al, 2010; Mori et al, 2007b; Seal et al, 2008), internal capsule (Buchsbaum et al, 1998; Lim et al, 1999), external capsule (Rotarska-Jagiela et al, 2009; Seal et al, 2008), cingulum (Kubicki et al, 2003; Mori et al, 2007b; Seok et al, 2007; Sun et al, 2003; Wang et al, 2004), fornix (Fitzsimmons et al, 2009; Kuroki et al, 2006), anterior commissure (Choi et al, 2011), arcuate fasciculus (Burns et al, 2003; Phillips et al, 2009), and cerebellar peduncles (Okugawa et al, 2006; Seok et al, 2007). Differences in RD are less examined, yet to date increases have been detected in the external capsule (Seal et al, 2008), in the left inferior temporal and left occipital lobe (Ashtari et al, 2007), in temporal WM (Koch et al, 2011), and in the middle cerebellar peduncle (Okugawa et al, 2006), and increased mean diffusivity has been detected in the splenium of the corpus callosum (Foong et al, 2000). The regions reported in these studies were also found in this work. For the most part, it appears that those studies with the largest sample sizes support the case of reduced microstructural organization in the interhemispheric, frontal deep and temporal WM fibers in schizophrenia, which is consistent with both the direction and regions implicated by the present findings.

The callosal microstructural deficits detected in vivo are supported by structural MRI and postmortem studies. The latter more specifically implicate several possible contributing factors to the abnormalities observed in schizophrenia in vivo studies. A structural MRI meta-analysis of 313 patients and 281 controls across 11 studies examining callosal morphometry detected reduced area but not length relative to controls (Woodruff et al, 1995). Postmortem studies have reported reductions in the corpus callosum (Highley et al, 1999a) and anterior commissure (Highley et al, 1999b) fiber number in schizophrenia and to a greater extent in females, although these findings are not consistently reported in the literature (Casanova et al, 1989), which may be a result of smaller sample sizes and increased heterogeneity in postmortem studies. Group differences detected in vivo in the UF (Burns et al, 2003; McIntosh et al, 2008; Miyata et al, 2010; Mori et al, 2007b; Seal et al, 2008) have not been supported by postmortem investigations, which report no differences fiber density and total fiber number in the UF between schizophrenia and control brains (Highley et al, 2002). In vivo and postmortem studies do concur on the right > left asymmetry in the UF. Finally, the fiber content (density multiplied by area) of the fornix did not differ significantly between schizophrenia and control groups (Chance et al, 1999).

The contributions of glial cell abnormalities to FA measured in vivo are not clear. Glial cells have a role in the activation of distinct intracellular pathways within neurons, to promote neuronal survival and axonal length (Wilkins et al, 2003). Abnormalities to glial cells could therefore plausibly contribute to dysmorphic axonal arrangement or packing density, which may affect the local anisotropy and diffusion signal. In schizophrenia, reduced oligodendrocyte-associated proteins (Flynn et al, 2003), fewer oligodendrocytes (Hof et al, 2003), and abnormal gene expression of key oligodendrocyte-related genes have been reported (Cotter et al, 2001; Flynn et al, 2003; Haroutunian et al, 2007; Hof et al, 2002; Tkachev et al,

2003). To date, the exact contribution of changes in axonal and support cell arrangement and packing on local anisotropy has not been directly assessed.

Finally, loss of myelin is a further potentially contributing factor in alterations in diffusion outcome parameters, presumably via increased cellular membrane permeability (Dyer, 2002). Diffusion anisotropy can be detected in the absence of myelin (Beaulieu, 2002), and the contribution of changes in myelin to altered diffusion measurements in vivo has been determined to be relatively low (Beaulieu, 2002, Beaulieu and Allen, 1994), with one study reporting a decrease of 20% in anisotropy in myelin-deficient animal models (Gulani et al, 2001). Nevertheless, in schizophrenia, myelination abnormalities have been demonstrated using MRI and T2 relaxation; reduced myelin water fraction was detected to a greater extent in the chronic than first episode groups and was localized to the genu of the corpus callosum and frontal WM (range 19–36%)(Flynn et al, 2003). Moreover, postmortem studies have detected 27% reduced immunoreactivity of myelin-associated glycoprotein (MAG) in the anterior frontal cortex (Flynn et al, 2003). Postmortem studies also provide evidence for myelin-related genetic abnormalities in schizophrenia indicating that oligodendrocyte and myelin genes are among the most prominently downregulated genes in schizophrenia (Hakak et al, 2001; Katsel et al, 2005). However, caution must be taken when interpreting in vivo dMRI results with reference to postmortem studies. Postmortem studies report results from more localized brain regions compared with the global dMRI analysis, as carried out in this study, and are usually carried out on smaller, more heterogeneous sample group compared with in vivo studies.

The analysis methods used in the above reviewed diffusion MRI studies in schizophrenia ranging from restricted to whole brain voxel-wise approaches, plus region of interest, based methods and the reconstruction of fibers by tracking methods. In addition, there is some variation in the acquisition parameters (number of directions, b-value), and in the eddy current and motion correction applied. Few studies to date have corrected for rotation of the b-matrix, which can introduce bias in orientation estimates and lead to reduced reliability of results (Leemans and Jones, 2009). We used a relatively high b-value (1300 s/mm$^2$), and used 64 diffusion gradients for accurate diffusion tensor estimation (Jones, 2004). Analysis involved a restricted set of skeleton-deep WM voxels (TBSS), which avoids problems associated with over-smoothing that otherwise impacts on the final results and increases the effect of partial volume (Jones et al, 2005).

Objective comparison of findings across existing studies is complicated by the clinical heterogeneity of the samples included within chronic schizophrenia, medication history, and medication exposure at the time of scanning. We have included a relatively homogenous group with a clinical profile of severe enduring schizophrenia despite being medicated with atypical antipsychotics, and who have never previously been exposed to clozapine. It remains possible that the deficits observed in the present and previous studies may be due to a history or current exposure to psychotropic medications. However, the present findings confirm that these deficits are detectable before exposure to clozapine, which has been previously demonstrated to have

structural effects on the brain (Ho *et al*, 2003; Molina *et al*, 2005; Scheepers *et al*, 2001). Nevertheless, it remains possible that typical and atypical antipsychotic medications contribute to deficits present at the time of scanning. Studies on drug-naive first episode patients also demonstrate reduced FA in patients with schizophrenia indicating that at least some of these WM abnormalities are likely to be related to the pathophysiology of schizophrenia (Cheung *et al*, 2008).

In conclusion, we detected localized reductions in FA with increases in RD in the corpus callosum and in the temporal lobe areas of cortico-cortical WM association tracts in a group of clozapine-naive treatment-resistant individuals with severe chronic schizophrenia that may be related negatively to the duration of illness. This may reflect reduced axonal number or packing density, cellular membrane abnormalities that increase permeability including possible loss of myelin, or inconsistent fiber orientation. These findings may be confounded by exposure to non-clozapine psychotropic medications; however, concurrent findings in studies involving subjects who are naive to psychotropic medication (Cheung *et al*, 2008; Gasparotti *et al*, 2009; Karlsgodt *et al*, 2009; Perez-Iglesias *et al*, 2010a; Zou *et al*, 2008) supporting the hypothesis that a portion of these deficits are due to the pathophysiology of schizophrenia. Postmortem studies provide support for a contribution of reduced axonal packing density, abnormal glial cell arrangement or function, and reduced myelin in schizophrenia. The extent to which these factors modulate the *in vivo* diffusion signal could be further informed by direct measurement of anisotropy in the healthy postmortem human brain and those with an antemortem diagnosis of schizophrenia.

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