Altered frontal white matter asymmetry and its implications for cognition in schizophrenia: A tractography study

Ainara Gómez-Gastiasoro, Leire Zubiaurre-Elorza, Javier Peña, Naroa Ibarretxe-Bilbao, Oiane Rilo, David J. Schretlen, Natalia Ojeda

Department of Methods and Experimental Psychology, Faculty of Psychology and Education, University of Deusto, Avenida de las Universidades, 24, 48007 Bilbao, Biscay, Spain

Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, 600 North Wolfe Street, Meyer 218, Baltimore, MD 21287-7218, United States

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ABSTRACT

Background: White matter (WM) alterations are well documented in schizophrenia. Abnormalities in inter-hemispheric fibers appear to account for altered WM asymmetry in the illness. However, the regional specificity (e.g., frontal versus occipital) of these alterations and their potential contribution to cognitive dysfunction in schizophrenia remain unknown.

Methods: Forty one patients with schizophrenia and 21 healthy controls (HC) underwent diffusion-weighted imaging on a 3 Tesla MRI machine. Tract-based spatial statistic (FSL) was used to assess whole brain differences in WM. Probabilistic tractography was performed in order to separately measure frontal and occipital WM tracts. Participants also completed tests of verbal memory and processing speed. Repeated measures analyses of covariance and Pearson correlation analyses were performed.

Results: A significant group x cerebral hemisphere interaction was found for fractional anisotropy (FA) ($F_{1,17} = 7.03; p = .017; \eta^2_p = 0.29$) and radial diffusivity (RD) ($F_{1,17} = 4.84; p = .042; \eta^2_p = 0.22$) in the frontal tract of patients versus HC. Healthy controls showed higher mean FA and lower mean RD in the left frontal tract compared to patients, who showed the opposite pattern. In patients with schizophrenia, mean FA and RD in the right frontal tract correlated with verbal memory ($r = −0.68, p = .046; r = 0.77, p = .015$).

Conclusions: Asymmetric WM alterations were found in a frontal tract of patients with schizophrenia. Higher mean FA in the right frontal tract correlated with worse verbal memory performance, suggesting a possible contribution these brain changes to cognitive impairment in schizophrenia.

1. Introduction

Abnormalities in white matter (WM) structural connectivity may contribute to cognitive impairment and clinical symptoms in schizophrenia (Friston and Frith, 1995; Friston, 1998; Dwork et al., 2007; Sui et al., 2015). These abnormalities especially involve medial frontal circuits (Ellison-Wright and Bullmore, 2009; Ellison-Wright et al., 2014; Mamah et al., 2010; Buchsbaum et al., 2006; Wheeler and Vocienkos, 2014). Two main regions of reduced WM integrity have been described in the left hemisphere of patients with schizophrenia. The first involves left frontal WM and includes WM interhemispheric fibers of the genu of the corpus callosum (gCC) among others. The second involves the left temporal WM and includes inter-hemispheric fibers via the splenium of the corpus callosum (sCC) (Ellison-Wright and Bullmore, 2009).

Interhemispheric fibers are altered in schizophrenia, possibly causing aberrant connectivity between the two cerebral hemispheres (Ellison-Wright et al., 2014; Wheeler and Vocienkos, 2014; Pol et al., 2004; Choi and al., 2011). The corpus callosum (CC) appears to be the most abnormal interhemispheric WM pathway in patients with schizophrenia (Ellison-Wright and Bullmore, 2009; Wheeler and Vocienkos, 2014; Raybaud, 2010; van der Knaap and van der Ham, 2011; Holleran et al., 2014). Decreased WM integrity in interhemispheric fibers also has been proposed to account for alterations of the normal brain asymmetry seen in these patients (Innocenti et al., 2003; Park et al., 2004; Ribolzi et al., 2014). Specifically, the hypoconnectivity in the CC has been proposed to contribute to altered asymmetry in persons with schizophrenia.
schizophrenia (van der Knaap and van der Ham, 2011). This could attenuate the normal leftward asymmetry of WM integrity commonly found in healthy controls (HC) in specific WM fibers (Park et al., 2004; Ribolsi et al., 2014; Miyata et al., 2012; Takao et al., 2010) such as the anterior corpus callosum (gCC) itself. The left-greater-than-right anisotropy asymmetry of the gCC seen in healthy adults is reduced in those with schizophrenia (Park et al., 2004).

Cognitive dysfunction afflicts most persons with schizophrenia, and impairments of simple processing speed and verbal memory are among the most widespread and severe (Heinrichs and Zakzanis, 1998; Mesholam-Gately et al., 2009). Cognitive dysfunction has been related to alterations in WM integrity in schizophrenia (Dwoork et al., 2007; Sui et al., 2015), but few studies have examined the possible relationship between the specific abnormalities in brain asymmetries and cognitive dysfunction in schizophrenia (see Antovna et al., 2004 for a review). Thus, alterations in length of the lateral sulcus, width of Sylvian fissure, and anterior frontal and occipital asymmetries seem to be related to performance on measures of expressive language, attention or verbal memory in patients (De Lisi et al., 1997; Hoff et al., 1992). In HC, WM brain asymmetries have been proposed to serve visuospatial functions, working memory, and especially language (Barrick et al., 2007; Catani et al., 2007; Powell et al., 2006). However, to our knowledge, no study has addressed the implications of the alterations in cerebral WM integrity asymmetry in anterior/frontal cortical projections (gCC) and posterior/occipital cortical projections (sCC) to cognitive dysfunction in persons with schizophrenia.

Diffusion weighted imaging (DWI), and specifically diffusion tractography, are powerful and sensitive tools to characterize WM abnormalities, and more precise than other approaches for identifying alterations in different brain structures in schizophrenia (Kana et al., 2006). Thus, tractography is a suitable technique and appropriate tool to study WM integrity of specific tracts. Using DWI, we first aimed to assess the whole brain WM integrity differences between patients with schizophrenia and HC. Secondly, we aimed to examine cerebral asymmetry in anterior frontal cortical projections of the gCC and posterior occipital cortical projections of the sCC in patients and HC by means of probabilistic tractography. This second aim was set based on the bibliography that claims that some of the brain asymmetry alterations in patients with schizophrenia could be caused by alterations in interhemispheric fibers such as the corpus callosum (van der Knaap and van der Ham, 2011; Innocenti et al., 2003; Park et al., 2004; Ribolsi et al., 2014) along with the localization of the two main areas of alterations described in Ellison-Wright and Bullmore’s meta-analysis (Ellison-Wright and Bullmore, 2009). Finally, we aimed to determine whether any observed differences in WM integrity asymmetry contribute to cognitive dysfunction in schizophrenia. We hypothesized that (1) patients with schizophrenia would show reduced WM integrity compared to HC specifically in fronto-temporal and occipital areas, (2) that WM asymmetry of patients would be altered compared to HC, and (3) that these alterations would correlate with cognitive dysfunction in patients with schizophrenia.

2. Materials and methods

2.1. Participants

Forty-one patients with schizophrenia (26 paranoid, 11 undifferentiated, 3 residual, and 1 disorganized) and 21 HC were recruited from the Baltimore site of the Bipolar-Schizophrenia Network on Intermediate Phenotypes study (B-SNIP) as described in Tamminga et al. (Tamminga et al., 2013). Patients’ inclusion criteria were: a) having schizophrenia diagnosis based on clinical data and the Structured Clinical Interview (SCID) for DSM-IV (First et al., 1997) and b) being clinically stable. HC were included if they had no diagnosis in axis I, also based on the SCID. Participants were excluded if they had: a) a known neurological illness or b) current substance use, detected or verified by urine toxicology screens. All the participants gave written informed consent to participate. The study was conducted following Declaration of Helsinki guidelines and was approved by the institutional review boards of all participating institutions.

2.2. Diffusion-weighted images

Diffusion-weighted images were obtained from a scanner placed at Baltimore (USA) as described in Skudlarski et al. (Skudlarski et al., 2013) (Supplemental Table S1). The scanner used single-shot spin-echo planar imaging (EPI) with a twice-refocused balance echo sequence. Diffusion image processing was performed using FSL software (Smith et al., 2004). Eddy current correction for distortions (Andersson and Sotiropoulos, 2016) was applied and the non-diffusion image (BO) was extracted. Brain Extraction Tool (BET) (Smith, 2002), was used to remove non-brain tissue. After that, fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), radial diffusivity (RD) and mode of anisotropy (MO) maps were generated by using DTIFIT, implemented in the FMRIB’s diffusion toolbox.

2.3. Tract-based spatial statistic

Tract-based spatial statistic (TBSS) (Smith et al., 2006) was used to assess group differences in FA, MD, AD, RD and MO. Using TBSS, data were prepared to apply a nonlinear registration of all FA images into standard space. The mean FA image was created using a threshold of 0.2 and thinned to create a “mean FA skeleton” which represents the centers of all tracts common to the group. MD, AD, RD and MO data were analyzed using “tbsf non FA” script, applying the original non linear registration to data and merging all subjects’ warped MD, AD, RD and MO data into a 4D file. This file was then projected onto the original mean FA skeleton to create the 4D-projected data. A subsample of 10 patients with schizophrenia and 10 HC was selected for tractography analyses based on the quality of their DWI. Only images with satisfactory quality for tractography were included in the analysis. The aforementioned process was performed in this subsample in order to obtain the whole brain overall FA values as well as the mean FA, MD, AD, RD and MO values of the different areas of the CC. Regions of interest (ROIs) of the gCC, the sCC and the body of the CC (bCC) were obtained from the Johns Hopkins University WM atlas. The obtained values were then exported to SPSS for further analyses.

2.4. Probabilistic tractography

Seeds and waypoint masks for tractography, gCC and frontal area, were extracted from the JHU atlas and Craddock atlas (Craddock et al., 2012), respectively. These were selected based on the whole brain results obtained after performed randomise. Thus, given that white matter differences were found in pathways of a left frontal area that included the gCC as the main interhemispheric fiber, gCC (both right and left separately) and a frontal area (the same area in both right and left hemisphere separately) were set as seed and waypoints masks respectively. After automatic registration between the selected mask and the FA map, gCC masks were manually corrected on each participant’s color-coded FA maps based on the MRI Atlas of Human White Matter (Oishi et al., 2010). WM pathways of interest were obtained after applying BedpostX and ProtrackX (implemented in FSL). Probabilistic connectivity distributions were generated from every voxel in the seed masks, and only those paths that went through the waypoint masks and stopped there were used for analysis. The anterior frontal cortical projections of the gCC were obtained for right and left hemispheres separately. All WM reconstructed trajectories were normalized by dividing by the number of streamlines that went through the waypoint masks and then thresholded at 5% (Fig. 1). The obtained anterior frontal cortical projections of the gCC included WM fibers from different pathways such as the forceps minor, the gCC, the cingulum, the
anterior corona radiata and the superior frontal gyrus. Tract-specific FA, MD, AD, RD and MO were obtained for each participant and exported to SPSS. The same process was used to obtain the posterior occipital cortical projections of the sCC interconnecting the sCC and occipital areas including fibers from the forceps major and the optic radiation (Fig. 1). Seeds and waypoints used to obtain this second pathway were set based on the second main area of white matter differences described in Ellison-Wright and Bullmore’s meta-analysis (Ellison-Wright and Bullmore, 2009) involving a left temporal area including fibers from the splenium of the corpus callosum and on the whole brain results obtained in the previous analyses.

2.5. Cognitive and clinical measures

Participants neuropsychological testing included measures of verbal memory and processing speed. Verbal memory was assessed using a combination of learning and delayed recall from the Hopkins Verbal Learning Test Revised (HVLT-R) (Benedict et al., 1998). Processing speed was assessed using the sum of letters (3 and 6) and patterns (3 and 6) of the Salthouse Perceptual Comparison Test (Salthouse and Babcock, 1991). In addition, the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) was used to assess patients’ clinical symptoms.

2.6. Statistical analyses

Normality of the variables was assessed with Shapiro-Wilk test and the following analyses were performed depending on the distribution of the variables. Group differences in sex, race, handedness, and DWI sequence were assessed with Chi-square analyses and Fisher’s exact test. Student t-tests were used to test for group differences in age and years of education. For neuroimaging analyses, whole WM brain differences in FA, MD, AD, RD and MO between 41 patients and 21 healthy controls were testing using the randomise tool (5000 permutations) with TFCE correction in FSL. Age, sex, race and DWI sequence were included as covariates, due to a software change during the project development. Significant regions were located and labelled anatomically with the MRI Atlas of Human White Matter (Oishi et al., 2010). Statistical threshold was set at $p < .05$ (FWE-corrected). MANCOVA was used to assess differences between the 10 patients with schizophrenia and 10 HC in gCC, bCC and sCC WM integrity. Repeated measures ANCOVA (including group as inter-subjects factor and laterality as intra-subjects factor) was used to examine group differences in the laterality of both anterior frontal cortical projections of the gCC and posterior occipital cortical projections of the sCC WM indexes (FA, MD, AD, RD and MO). Partial correlations were performed in order to assess the relationship between both right and left anterior frontal cortical projections of the gCC and posterior occipital cortical projections of the sCC WM indexes and cognitive performance separately in patients with schizophrenia and HC. Whole brain overall FA values were entered as a covariate in all the analyses. All the analyses were performed using SPSS v.23.

3. Results

3.1. Sociodemographic and clinical variables

Sociodemographic and clinical variables of the whole sample (41 patients and 21 HC) are shown in Table 1. No differences were observed between patients with schizophrenia and HC in age, handedness, race, or years of education. The schizophrenia group had a higher proportion of men than the HC group, as expected (Häfner, 1997). In the smaller tractography subsamples (10 patients and 10 HC), no group differences were found in age, years of education, sex, race, handedness, or DWI scan used to acquire images based on Student’s t and Fisher’s exact tests (Table 2).

3.2. Whole brain differences in WM indexes

Patients with schizophrenia showed lower mean FA than HC in a well-delimited area of the left frontal lobe (FWE-corrected, $p < .05$) (Table 3; Fig. 2). No differences were found for MD, AD, RD or MO.
3.3. Differences in WM indexes of the CC

Regarding differences in WM mean FA of the three specific areas of the CC, patients with schizophrenia showed lower mean FA than HC in the gCC \((F = 6.48; p = .021)\). No significant results were found when assessing the differences in other integrity measures of the gCC (MD, AD, RD or MO). No differences were observed in relation to the bCC or the sCC in any of the WM integrity indexes (Table 4).

3.4. Group differences in tract asymmetry

Repeated measures ANCOVA revealed a statistically significant group x hemisphere interaction for mean FA in anterior frontal cortical projections of the gCC \((F_{1,17} = 7.03; p = .017; \eta^2 = 0.29)\). That is, the HC group showed higher mean FA in the left than right anterior frontal cortical projections of the gCC (M = 0.49; SE = 0.01 versus M = 0.47; SE = 0.01), while patients with schizophrenia showed higher mean FA in the right than left anterior frontal cortical projections of the gCC (M = 0.51; SE = 0.01 versus M = 0.49; SE = 0.01). In addition, a group x hemispheric laterality effect was also found for mean RD \((F_{1,17} = 4.84; p = .042; \eta^2 = 0.22)\). In this case, healthy controls showed lower mean RD in the left than right hemisphere tracts (M = 0.54 \times 10^{-3}; SE = 0.10 \times 10^{-4} versus M = 0.56 \times 10^{-3}; SE = 0.12 \times 10^{-4}). Patients with schizophrenia showed lower mean RD in the right than left hemisphere tract (M = 0.52 \times 10^{-3}; SE = 0.12 \times 10^{-4} versus M = 0.54 \times 10^{-3}; SE = 0.10 \times 10^{-4}). No

### Table 1

|                | SZ (n = 41) | HC (n = 21) | \(\chi^2\) | 95% CI     | \(p\) |
|----------------|-------------|-------------|------------|------------|------|
| **Age**        |             |             |            |            |      |
| Male           | 29 (70.73)  | 6 (28.57)   | 10.04      | \([-0.90\) 11.91\] | 0.002 |
| **Years of education** | 13.33 (2.58) | 14.52 (1.94) | 1.95       | \([-0.09\) 2.48\] | 0.067 |
| **Handedness** |             |             |            |            |      |
| Right          | 35 (85.36)  | 17 (80.95)  | 1.99       | \[-0.09\) 2.48\] | 0.371 |
| Left           | 4 (9.76)    | 4 (19.05)   |            |            |      |
| Both           | 2 (4.88)    | 0 (0.00)    |            |            |      |
| **Race**       |             |             |            |            |      |
| Black          | 25 (60.98)  | 8 (38.10)   | 2.92       | \[-0.09\) 2.48\] | 0.087 |
| White          | 16 (39.02)  | 13 (61.90)  |            |            |      |
| **Age of onset** |             |             |            |            |      |
| 21.78 (8.17)   |             |             |            |            |      |
| **Illness duration** | 16.00 (11.95) |             |            |            |      |
| **DWI TR**     |             |             |            |            |      |
| 6700 ms        | 37 (90.24)  | 19 (90.48)  | 0.001      | \[-0.09\) 2.48\] | 0.977 |
| 6300 ms        | 4 (9.76)    | 2 (9.52)    |            |            |      |
| **SGAs**       |             |             |            |            |      |
| Yes            | 35 (85.37)  |             |            |            |      |
| No             | 6 (14.63)   |             |            |            |      |
| **FGAs**       |             |             |            |            |      |
| Yes            | 6 (14.63)   |             |            |            |      |
| No             | 35 (85.37)  |             |            |            |      |
| **PANSS**      |             |             |            |            |      |
| Positive       | 14.44 (6.17)|             |            |            |      |
| Negative       | 15.76 (5.53)|             |            |            |      |
| General        | 25.51 (5.75)|             |            |            |      |

SZ, schizophrenia; HC, healthy controls; SD, standard deviation; n, sample size; \(\chi^2\), Chi square; CI, confidence interval; LL, lower limit; UL, upper limit; DWI, diffusion weighted imaging; TR, repetition time; ms, milliseconds; SGAs, second-generation antipsychotics; FGAs, first-generation antipsychotics; PANSS, positive and negative syndrome scale.

### Table 2

|                | SZ (n = 41) | HC (n = 21) | \(\chi^2\) | 95% CI     | \(p\) |
|----------------|-------------|-------------|------------|------------|------|
| **Age**        |             |             |            |            |      |
| Male           | 29 (70.73)  | 6 (28.57)   | 10.04      | \([-0.90\) 11.91\] | 0.002 |
| **Years of education** | 13.33 (2.58) | 14.52 (1.94) | 1.95       | \([-0.09\) 2.48\] | 0.067 |
| **Handedness** |             |             |            |            |      |
| Right          | 35 (85.36)  | 17 (80.95)  | 1.99       | \([-0.09\) 2.48\] | 0.371 |
| Left           | 4 (9.76)    | 4 (19.05)   |            |            |      |
| Both           | 2 (4.88)    | 0 (0.00)    |            |            |      |
| **Race**       |             |             |            |            |      |
| Black          | 25 (60.98)  | 8 (38.10)   | 2.92       | \([-0.09\) 2.48\] | 0.087 |
| White          | 16 (39.02)  | 13 (61.90)  |            |            |      |
| **Age of onset** |             |             |            |            |      |
| 21.78 (8.17)   |             |             |            |            |      |
| **Illness duration** | 16.00 (11.95) |             |            |            |      |
| **DWI TR**     |             |             |            |            |      |
| 6700 ms        | 37 (90.24)  | 19 (90.48)  | 0.001      | \[-0.09\) 2.48\] | 0.977 |
| 6300 ms        | 4 (9.76)    | 2 (9.52)    |            |            |      |
| **SGAs**       |             |             |            |            |      |
| Yes            | 35 (85.37)  |             |            |            |      |
| No             | 6 (14.63)   |             |            |            |      |
| **FGAs**       |             |             |            |            |      |
| Yes            | 6 (14.63)   |             |            |            |      |
| No             | 35 (85.37)  |             |            |            |      |
| **PANSS**      |             |             |            |            |      |
| Positive       | 14.44 (6.17)|             |            |            |      |
| Negative       | 15.76 (5.53)|             |            |            |      |
| General        | 25.51 (5.75)|             |            |            |      |

SZ, schizophrenia; HC, healthy controls; SD, standard deviation; n, sample size; \(\chi^2\), Chi square; CI, confidence interval; LL, lower limit; UL, upper limit; DWI, diffusion weighted imaging; TR, repetition time; ms, milliseconds; SGAs, second-generation antipsychotics; FGAs, first-generation antipsychotics; PANSS, positive and negative syndrome scale.
significant group differences were found for AD, MD or MO (Table 5).

3.5. Correlations between WM tracts and cognition

Correlation analyses were performed only for those WM indexes in which a significant group x hemispheric laterality effect was found. In patients with schizophrenia, verbal memory performance correlated inversely with mean FA of the right gCC tract ($r = -0.68, p = .046$) (Fig. 3a), indicating higher mean FA correlated with worse verbal memory performance in patients with schizophrenia. Further, verbal memory performance correlated positively with mean RD of the right anterior frontal cortical projections of the gCC ($r = 0.77, p = .015$) (Fig. 3b), indicating that higher mean RD correlated with better verbal memory. No significant correlations were found regarding processing speed. No significant results were found in HC group (Fig. 3c and d).

4. Discussion

This study aimed firstly to elucidate whole brain WM integrity differences between persons with schizophrenia and HC, secondly to test for group differences in WM asymmetry of both anterior frontal (gCC) and posterior occipital (sCC) cortical projections of the corpus callosum, and thirdly to assess their relationship with cognitive dysfunction in patients.

As expected, whole brain analyses revealed that patients with schizophrenia had lower mean FA than healthy controls in a well-delimited region of the left frontal lobe. Specifically, these group differences included the anterior corona radiata, anterior limb of the internal capsule (anterior thalamic radiation and inferior fronto-occipital fasciculus) external capsule (inferior fronto-occipital fasciculus) inferior and superior frontal gyrus white matter.

HC, healthy controls; SZ, schizophrenia.

FSL coordinates indicate: x increases from left to right; y increases from posterior to anterior; and z increases from inferior to superior.

Region in bold represents the maximum coordinate encompassed in the given cluster.

HC > patients with SZ.

| FSL coordinates | Cluster size (voxels) | x | y | z | p | Anatomical brain regions |
|-----------------|-----------------------|---|---|---|---|-------------------------|
| HC > SZ         | 871                   | 117| 158| 81| 0.023 | Left anterior corona radiata |
|                 |                       |   |   |   |     | anterior limb of the internal capsule (anterior thalamic radiation and inferior fronto-occipital fasciculus) external capsule (inferior fronto-occipital fasciculus) inferior and superior frontal gyrus white matter |
|                 |                       |   |   |   |     | genu of the corpus callosum |
|                 |                       |   |   |   |     | cingulum |

Table 3
Cluster characteristics of the whole brain differences in mean FA between patients with schizophrenia and HC.

HC, healthy controls; SZ, schizophrenia.

FSL coordinates indicate: x increases from left to right; y increases from posterior to anterior; and z increases from inferior to superior.

Region in bold represents the maximum coordinate encompassed in the given cluster.

HC > patients with SZ.

Fig. 2. Whole brain FA differences between patients with schizophrenia and HC. Differences are significant at $p < .05$ corrected for family-wise error (FWE). WM regions in which patients with schizophrenia showed a lower mean FA compared to HC are shown in red-yellow; the WM skeleton is shown in green. R, right; L, left; FA, fractional anisotropy; WM, white matter; SZ, schizophrenia; HC, healthy controls.
The origin of brain asymmetry is a matter of enduring scientific interest, and many experts believe that both genetic and environmental factors contribute to its development (Jahanshad et al., 2010; Toga and Thompson, 2003). Thus, up to 30% of the leftward asymmetry of some WM fibers (i.e., the inferior fronto-occipital fasciculus and anterior thalamic radiation or forceps major) has been attributed to genetic factors. Conversely, environmental factors have shown to account for about 10% of the variance in the asymmetry of other regions such as the forceps minor (Jahanshad et al., 2010). In addition, asymmetries of the right frontal and temporal lobes volumes appear to be more influenced by genetic factors than contralateral volumes of the same regions, which seem to be more affected by environmental features, and the occipital lobe seems to show lower heritability overall (Geschwind et al., 2002). In addition, asymmetries of the right frontal and temporal lobes volumes appear to be more influenced by genetic factors than contralateral volumes of the same regions, which seem to be more affected by environmental features, and the occipital lobe seems to show lower heritability overall (Geschwind et al., 2002). Taking this into account, asymmetry alterations of those brain regions that demonstrate heritability might be used as intermediate phenotypes to guide the search for new genes related to the disease (Lenroot et al., 2009).

While speculative, results regarding the relationship between a higher FA of the right frontal cortical projections of the gCC and worse verbal memory in patients with schizophrenia might result

Table 4

| Variable            | SZ (n = 10) | 95% CI | HC (n = 10) | 95% CI | F     | p     | η²  |
|---------------------|------------|--------|------------|--------|-------|-------|-----|
|                     | M (SE)     | LL     | UL         | M (SE) | LL    | UL    |     |
| gCC                 | 0.152 (0.001) | 0.150  | 0.154      | 0.155 (0.001) | 0.153 | 0.157 | 6.481 | 0.021 | 0.276 |
| bCC                 | 0.153 (0.002) | 0.148  | 0.158      | 0.154 (0.002) | 0.149 | 0.159 | 1.655 | 0.199 | 0.100 |
| sCC                 | 0.147 (0.001) | 0.145  | 0.148      | 0.146 (0.001) | 0.144 | 0.147 | 0.923 | 0.350 | 0.052 |

SZ, schizophrenia; HC, healthy controls; SE, standard error; n, sample; CI, confidence interval; LL, lower limit; UL, upper limit; F, MANCOVA; gCC, genu of the corpus callosum; bCC, body of the corpus callosum; sCC, splenium of the corpus callosum; η²: partial eta-squared.

Table 5

Repeated measures ANCOVA assessing asymmetry differences between patients with schizophrenia and healthy controls in the anterior frontal cortical projections of the genu of the corpus callosum.

| Variable            | SZ (n = 10) | 95% CI | HC (n = 10) | 95% CI | F     | p     | η²  |
|---------------------|------------|--------|------------|--------|-------|-------|-----|
|                     | M (SE)     | LL     | UL         | M (SE) | LL    | UL    |     |
| AFCpgCC FA          | 0.51 (0.01) | 0.47   | 0.51       | 0.47   | 0.51  | 0.735 | 0.017 | 0.29 |
| AFCpgCC RD          | 0.49 (0.01) | 0.49    | 0.49       | 0.49   | 0.49  | 1.000 | 0.318 | 0.06 |
| AFCpgCC MO          | 0.42 (0.03) | 0.37   | 0.42       | 0.39   | 0.39  | 1.000 | 0.318 | 0.06 |

AFCpgCC, anterior frontal cortical projections of the genu of the corpus callosum; SZ, Schizophrenia; HC, healthy controls; SE, standard error; η²: partial eta square. No interaction effect was found for FA when assessing asymmetry of the posterior occipital cortical projections of the sCC (F = 4.07; p = .06). Therefore, the other indexes were not analyzed.
from an abnormality in axonal pruning that affects cognitive development. Others have suggested that deficient axonal pruning might decrease information transmission efficiency by producing redundant brain networks (Alba-Ferrara and De Erausquin, 2013). Thus, one could hypothesize that deficient pruning contributes to increased mean FA and decreased cognitive efficiency in these patients, as found in the present study. In short, the obtained results suggest that abnormalities in WM integrity of right frontal areas, such as anterior frontal cortical projections of the gCC, could reflect a neuroanatomic substrate of verbal memory impairment in schizophrenia.

We also found that higher mean RD in right anterior frontal cortical projections of the gCC correlated with a better verbal memory performance in patients. RD has been related to demyelination process (Alexander et al., 2007). Typically, increases in FA are accompanied by decreases in all other diffusion indices (MD, AD, and RD). In schizophrenia, both mean FA and RD follow an atypical development pattern. Therefore, and inversely to the relationship found between mean FA and verbal memory, higher mean RD shows a relationship with better information transmission efficiency.

We failed to find a significant relationship between processing speed and WM integrity of the anterior frontal cortical projections of the gCC. This might be explained by the fact that these WM fibers are located in the medial prefrontal regions of the brain. Given that processing speed tasks engage many cognitive processes, it is reasonable to expect that performance on them will depend on more widely distributed WM abnormalities in periventricular and other subcortical tracts than anterior frontal cortical projections of the gCC (Magistro et al., 2015; Penke et al., 2010; Vernooij et al., 2009). This added to the previously mentioned relationship between brain asymmetry alterations and language in schizophrenia could explain why only verbal memory seemed to be related with the WM integrity asymmetry of this tract.

Results obtained in the present study must be seen in the context of its limitations. First, the small sample, especially in tractography analyses, limits generalization to schizophrenia in general. As noted above, these findings should be viewed as preliminary but potentially useful insofar as they suggest some direction for future research. Second, while tractography is thought to be a powerful tool for studying WM integrity in schizophrenia and other populations, an important limitation of it relates to the existence of crossing fibers that influence FA and, therefore, might contribute to the present findings. The bending, merging and crossing of fibers in some voxels together with low spatial resolution at 3 T could lead to inexact measures of FA (Dell’Acqua and Catani, 2012). Third, possible medication and illness duration effects are not taking into account in the analyses. Future research, and specifically longitudinal studies, should investigate the influence of medication and illness duration on the relationship between WM asymmetry alterations and cognition in schizophrenia. Finally, due to the reduced sample, we were unable to assess the possible differences between left- and right-handed patients groups in terms of brain asymmetry and its relationship with cognition. Future studies should assess if handedness has a specific role in the relationship between brain asymmetry alterations and cognition in patients with schizophrenia.
Despite these limitations, the present findings suggest that aberrant WM asymmetry might contribute to a central form of cognitive dys-function in schizophrenia, one that entails both language processing and episodic memory. This could help to design more specific cognitive rehabilitation interventions that account for this putative neuroanatomical basis of impaired verbal learning and memory. Finally, combination of reversed asymmetry in specified WM tracts and impaired verbal learning/memory might serve as a useful marker of schizophrenia if future research shows that it has both sensitivity and specificity for diagnosis.

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Declarations of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclineuro.2019.101781.

References

Agartz, I., Andersson, J.L., Skare, S., 2001. Abnormal brain white matter in schizophrenia: a diffusion tensor imaging study. Neuroreport 12, 2251–2254.

Alba-Ferrara, L., De Erazquin, G.A., 2013. What does anisotropy measure? Insights from increased and decreased anisotropy in selective fiber tracts in schizophrenia. Front. Integr. Neurosci. 7, 1–5.

Alexander, A.L., Lee, J.E., Lazar, M., Field, A.S., 2007. Diffusion tensor imaging of the brain. Neurotherapeutics 4, 316–329.

Anderson, J.L., Sotiriopoulos, S.N., 2016. An integrated approach to correction for off-resonance effects and subject movement in diffusion MR imaging. Neuroimage 125, 1063–1078.

Antonova, E., Sharma, T., Uddin, L., Knutson, K., 2014. Anomalous cerebral asymmetry and language processing in schizophrenia. Anomalous lateral sulcus asymmetry and cognitive function in first-episode schizophrenia. Schizophr. Bull. 18, 207–272.

Bartzokis, G., Lu, P.H., Heydari, P., Couvrette, A., Lee, G.J., Kalashyan, G., et al., 2012. Multimodal magnetic resonance imaging assessment of white matter aging trajectories over the lifespan of healthy individuals. Biol. Psychiatry 72, 1026–1034.

Benedict, R.H., Schretlen, D., Groningen, L., Brandt, J., 1998. hippocampus b) and impaired verbal learning/cognition: a neuropsychological study of the genetic basis of the disease. Arch. Gen. Psychiatry 46, 1145–1150.
Kubicki, M., Stynier, M., Bouix, S., Gereg, G., Markant, D., Smith, K., et al., 2008. Reduced interhemispheric connectivity in schizophrenia-tractography based segmentation of the corpus callosum. Schizophr. Res. 106, 125–131.

Lebel, C., Walker, L., Leemans, A., Phillips, L., Beaulieu, C., 2008. Microstructural maturation of the human brain from childhood to adulthood. Neuroimage 40, 1044–1055.

Lenroot, R.K., Schmitt, J.E., Ondarz, S.J., Wallace, G.L., Neale, M.C., Lerch, J.P., et al., 2009. Differences in genetic and environmental influences on the human cerebral cortex associated with development during childhood and adolescence. Hum. Brain Mapp. 30, 163–174.

Magistro, D., Takeuchi, H., Nejad, K.K., Taki, Y., Sekiguchi, A., Nouchi, R., et al., 2015. The relationship between processing speed and regional white matter volume in healthy young people. PLoS ONE 10, e0136486.

Mamah, D., Conturo, T.E., Harms, M.P., Akbudak, E., Wang, L., McMichael, A.R., et al., 2010. Anterior thalamic radiation integrity in schizophrenia: a diffusion-tensor imaging study. Psychiatry Res. Neuroimaging 183, 144–150.

Menholm-Gately, R.L., Giuliano, A.J., Goff, K.P., Faraone, S.V., Seidman, L.J., 2009. Neurocognition in first-episode schizophrenia: a meta-analytic review. Neuropsychology 23, 315–336.

Mitchell, R.L., Crow, T.J., 2005. Right hemisphere language functions and schizophrenia: the forgotten hemisphere? Brain 128, 963–978.

Miya, K., Sasamoto, A., Koelkebeck, K., Hirao, K., Ueda, K., Kawada, R., et al., 2012. Abnormal asymmetry of white matter integrity in schizophrenia revealed by voxel-wise diffusion tensor imaging. Hum. Brain Mapp. 33, 1741–1749.

Oishi, K., Faria, A.V., van Zijl, P.C., Mori, S., 2010. MRI Atlas of Human White Matter. Academic Press.

Park, H., Westin, C., Kubicki, M., Maier, S.E., Niznikiewicz, M., Baer, A., et al., 2004. Focal white matter density changes in schizophrenia: reduced inter-hemispheric connectivity. Neuroimage 23, 213–223.

Pearlson, G.D., Folley, B.S., 2008. Schizophrenia, psychiatric genetics, and darwinian psychiatry: an evolutionary framework. Schizophr. Bull. 34, 722–733.

Penke, L., Munoz Maniega, S., Murray, C., Gow, A.J., Hernandez, M.C., Clayton, J.D., et al., 2010. A general factor of brain white matter integrity predicts information processing speed in healthy older people. J. Neurosci. 30, 7569–7574.

Poli, H.E., Schucn, H.G., Mandi, R.C., Caba, W., Collins, D.L., Evans, A.C., Kahn, R.S., 2004. Focal white matter density changes in schizophrenia: reduced inter-hemispheric connectivity. Neuroimage 21, 37–35.

Powell, H.R., Parker, G.J., Alexander, D.C., Symms, M.R., Bolby, P.A., Wheeler-Kingshott, C.A., et al., 2006. Hemispheric asymmetries in language-related pathways: a combined functional MRI and tractography study. Neuroimage 32, 388–399.

Price, G., Cercignani, M., Parker, G.J., Altmann, D.R., Barnes, T.R., Barker, G.J., et al., 2007. Abnormal brain connectivity in first-episode psychosis: a diffusion MRI tractography study of the corpus callosum. Neuroimage 35, 458–466.

Pujo, J., Vendrell, P., Junqué, C., Martí-Vilalta, J.I., Capdevila, A., 1993. When does human brain development end? evidence of corpus callosum growth up to adulthood. Ann. Neurol. 34, 71–75.

Raybaut, C., 2010. The corpus callosum, the other great forebrain commissures, and the septum pellucidum: anatomy, development, and malformation. Neuroradiology 52, 447–477.

Ribon, M., Daskalakis, Z.J., Siracusano, A., Koch, G., 2014. Abnormal asymmetry of brain connectivity in schizophrenia. Front. Hum. Neurosci. 8, 1–11.

Salhouse, T.A., Babcock, R.L., 1991. Decomposing adult age differences in working memory. Dev. Psychol. 27, 763.

Skudlarski, P., Schredl, D.J., Thaker, G.K., Stevens, M.C., Keshavan, M.S., Sweeney, J.A., et al., 2013. Diffusion tensor imaging white matter endophenotypes in patients with schizophrenia or psychotic bipolar disorder and their relatives. Am. J. Psychiatry 170, 886–898.

Smith, S.M., 2002. Fast robust automated brain extraction. Hum. Brain Mapp. 17, 143–155.

Smith, S.M., Jenkinson, M., Woolrich, M.W., Beckmann, C.F., Behrens, T.E., Johansen-Berg, H., et al., 2004. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage 23, S208–S219.

Smith, S.M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T.E., Mackay, C.E., et al., 2006. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. Neuroimage 31, 1487–1505.

Sui, J., Pearson, G.D., Du, Y., Yu, Q., Jones, T.R., Chen, J., et al., 2015. In search of multimodal neuroimaging biomarkers of cognitive deficits in schizophrenia. Biol. Psychiatry 78, 794–804.

Takao, H., Abe, D., Yamase, H., Aoki, S., Kasai, K., Ohtomo, K., 2010. Cerebral asymmetry in patients with schizophrenia: a voxel-based morphometry (VBM) and diffusion tensor imaging (DTI) study. J. Magn. Reson. Imaging. Imaging 31, 221–226.

Tamminga, C.A., Ileva, E.I., Keshavan, M.S., Pearlson, G.D., Clementz, B.A., Witte, B., et al., 2013. Clinical phenotypes of psychosis in the bipolar-schizophrenia network on intermediate phenotypes (B-SNIP). Am. J. Psychiatry 170, 1263–1274.

Toga, A.W., Thompson, P.M., 2003. Mapping brain asymmetry. Nat. Rev. Neurosci. 4, 37–48.

van der Knaap, L., van der Ham, I., 2011. How does the corpus callosum mediate interhemispheric transfer? A review. Behav. Brain Res. 223, 211–221.

Vernooij, M.W., Ikram, M.A., Vrooman, H.A., Wielopolski, P.A., Krestin, G.P., Hofman, A., et al., 2009. White matter microstructural integrity and cognitive function in a general elderly population. Arch. Gen. Psychiatry 78, 143–155.

Wheeler, A.L., Voineskos, A.N., 2014. A review of structural neuroimaging in schizophrenia: from connectivity to connectomics. Front. Hum. Neurosci. 8, 1–18.