Psychiatry Research: Neuroimaging 291 (2019) 63–70

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Corpus callosum microstructural and macrostructural abnormalities in schizophrenia according to the stage of disease

Jérémy Madigand[a,b,c,1], Maxime Tréhout[a,b,c,1], Nicolas Delcroix[d,2], Sonia Dollfus[a,b,c,1], Elise Leroux[a,*]

[a] Normandie Univ, UNICAEN, ISTS EA 7466, GIP CYCERON, Caen F-14000, France
[b] CHU de Caen, Service de psychiatrie Adulte, Centre Esquirol, Caen F-14000, France
[c] Normandie Univ, UNICAEN, UFR de Médecine (Medical School), Caen F-14000, France
[d] Normandie Univ, UNICAEN, CNRS, UMS GIP CYCERON, Caen F-14000, France

ARTICLE INFO

Keywords:
Schizophrenia
Corpus callosum
Diffusion tensor imaging
Magnetic resonance imaging
White matter
Volume

ABSTRACT

Corpus callosum (CC) volume and surface (macrostructural) studies remain controversial and have not considered the illness duration (ID) systematically. Regardless of ID, some CC macrostructural studies have shown no difference between SZ patients and healthy controls (HC), whereas others have reported macrostructural abnormalities in SZ. Conversely, CC microstructural studies are more in agreement with alterations in CC integrity regardless of the patients' ID, but the direction and degree of these abnormalities over time remain unknown. Moreover, no study has explored both the micro- and macrostructure of the CC in SZ by considering the stage of disease. Both CC micro- and macrostructural data were investigated in 43 SZ patients and compared between two patient groups (21 patients with a short ID and 22 with a long ID) and HC (23 participants) using diffusion tensor and structural imaging. CC microstructural alterations were detected in both SZ groups compared to the HC group, without differences between the SZ groups. In contrast, CC macrostructural alterations were only found in the long ID group. CC microstructural alterations might be detected in schizophrenia at an early stage, without an increase of magnitude thereafter, while CC macrostructural alterations might become apparent at later stages of the illness.

1. Introduction

The corpus callosum (CC), the main commissure of the white matter (WM), has been particularly implicated in the pathophysiology of schizophrenia and has been described as altered in this disorder (Ublinskii et al., 2015). The CC enhances the transfer and integration of high-level cognitive information, such as language and executive functions (Gazzaniga, 2000). However, studies on callosal volume and cross-sectional surface area (macrostructure) using magnetic resonance imaging (MRI) in schizophrenia remain controversial and have not considered the illness duration systematically. Regardless of the illness duration, some studies have indeed shown no difference between patients with schizophrenia (SZ) and healthy controls (HC) groups (Chua et al., 2000; Frumin et al., 2002; Lei et al., 2015; Trehout et al., 2017; Woodruff et al., 1997), whereas others have reported macrostructural abnormalities (Balevich et al., 2015; Collinson et al., 2014; Downhill et al., 2000; John et al., 2008; Knochel et al., 2012b). Among the only studies that have already considered the stage of disease as Walterfang et al. (2008), Arnone et al. (2008) or Johnson et al. (2013), the results remain discrepant. Indeed, Walterfang et al. (2008) found no significant difference in CC total area across first-episode, chronic SZ and HC groups. This result is in agreement with Johnson et al. (2013) that reported no callosal surface difference between childhood-onset SZ patients and HC. Conversely, the meta-analysis by Arnone et al. (2008) found callosal decrease in both SZ group and first-episode psychosis subgroup compared to their respective HC groups. However, the meta-analysis by Arnone et al. (2008) included only four studies in first-episode patients and their results were in contradiction with other studies (Walterfang et al., 2008; Johnson et al., 2013). Therefore, the macrostructural results might be more in agreement when the illness

* Corresponding author at: GIP CYCERON, Campus Jules Horowitz, Bd Henri Becquerel, BP 5229, F-14074 Caen, France.
E-mail addresses: madigand-j@chu-caen.fr (J. Madigand), trehout-m@chu-caen.fr (M. Tréhout), Nicolas.DELCROIX@cnrs.fr (N. Delcroix), dollfus-s@chu-caen.fr (S. Dollfus), eleroux@cyceron.fr (E. Leroux).
[1] Present address. Centre Hospitalier Universitaire, Centre Esquirol, 14000 Caen, France.
[2] Present address. GIP CYCERON, Campus Jules Horowitz, Bd Henri Becquerel, BP 5229, F-14074 Caen, France.

https://doi.org/10.1016/j.pscychresns.2019.08.002
Received 28 February 2019; Received in revised form 5 August 2019; Accepted 5 August 2019
Available online 06 August 2019

duration of SZ is considered since abnormalities might appear or be detected at a late stage of disease. In contrast, microstructural studies using diffusion tensor imaging (DTI) are more consistent, whatever the stage of illness in SZ (Zhuo et al., 2016), although the evolution of these abnormalities remains unknown.

To date, no study has explored both micro- and macrostructure in SZ by considering the stage of disease. Our hypothesis is that the CC macrostructural abnormalities may be essentially detected at a late stage of the disease, whereas the CC microstructural abnormalities would be detected at an earlier stage. To support this hypothesis, this study aims to compare both callosal micro- and macrostructural data in two groups of SZ patients (short and long illness duration) and a HC group. The callosal regions involved in audition, language and executive functions were targeted since these functions are known to be impaired in SZ (Cavelti et al., 2018; de et al., 2003; Vroomen and de, 2003; Wigand et al., 2015).

2. Methods

2.1. Participants

Three participant groups were included: one stabilized SZ group (*i.e.* patients without any change in their antipsychotic medication for at least one month) with a short illness duration (SID, $n = 21$), one stabilized SZ group with a long illness duration (LID, $n = 22$) and one HC group ($n = 23$). The SZ groups were determined on the global median of illness duration in all SZ patients to obtain two equivalent patient samples (median illness duration = 10.7 years) in order to analyse the CC micro- and macrostructure by considering the stage of disease. The illness duration was calculated as the duration between the date of the first hospitalisation for SZ symptomatology and the date of the imaging investigation. When there were no past hospitalisations, the date of psychotic symptoms onset reported in the medical report was used.

The three groups did not significantly differ in gender and education level (Table 1). All participants were right-handed (*i.e.*, with an Oldfield score greater than 50 (Oldfield, 1971)) to limit confounding factors in the statistical analyses. The diagnosis of SZ was established according to the DSM-IV criteria (Diagnostic and Statistical Manual of Mental Disorder 4th edition) and the MINI semi-structured interview (Mini International Neuropsychiatric Interview). Antipsychotic drug use was stable during the month preceding inclusion in the study. Both SZ groups did not significantly differ in medication in chlorpromazine equivalent (Table 1). The psychopathological status of SZ was examined using PANSS (Positive And Negative Syndrome Scale; (Kay et al., 1987)). The characteristics of participants (illness duration (ID), age, gender, medication in chlorpromazine equivalent, type of antipsychotic medication and PANSS scores) are available in the Table 1.

SZ patients were recruited from the University Hospital (Caen, France), and participants for the HC group were recruited from the community. All participants were free of auditory deficits, neurological disorders, and cerebral abnormalities. All participants gave informed written consent in accordance with the Declaration of Helsinki, and the local ethics committee (Comité de Protection des Personnes Nord-Ouest, France) approved the experimental protocol.

2.2. Acquisition and preprocessing of the imaging data

The native neuroimaging data were acquired using a 3T scanner (Intera Achieva, Philips Medical System, Netherlands). Three-dimensional, high-resolution T_1-weighted brain volume were acquired (3D-FFE-TFE sequence; 256 × 256 matrix size with 180 contiguous slices; 256 mm field of view (FOV); 1 mm isotropic resolution; sagittal slice orientation; 20 ms repetition time (RT); 4.6 ms echo time (ET); 10° flip angle (FA); 800 ms inversion time; and a SENSE factor of 2). A T_2-weighted scan was also acquired for each participant (T2-TSE sequence; 256 × 256 matrix size with 81 contiguous slices; 256 mm FOV; 2 mm isotropic resolution; sagittal slice orientation; 5500 ms RT; 80 ms ET; 90°FA; and a SENSE factor of 2). Diffusion-weighted images (DWI from DTI) were obtained using a DWI sequence from 21 directions with one image without diffusion weighting (factor $b = 1000$ s/mm2; 112 × 112 matrix size with 70 contiguous slices; 224 mm FOV; 2 mm isotropic resolution; axial slice orientation; 8500 ms RT; 81 ms ET; 90°FA; and a SENSE factor of 2.5).

Regarding preprocessing of the macrostructural data, we used SPM software subroutines (Statistical Parametric Mapping, Wellcome Department of Cognitive Neurology, London, UK, http://www.fil.ion.ucl.ac.uk/spm) to obtain segmented and modulated WM images from the T_1 images. Regarding the microstructural data, the method used to extract diffusion maps has already been published previously (Leroux et al., 2013; Leroux et al., 2014). Briefly, diffusion maps of anisotropy fractional (FA) as well as radial and mean diffusivities (RD and MD in mm^2/s, respectively) for each participant (DTIFIT, FMRIB's Diffusion Toolbox: FDT) were obtained from FSL software (FLIRT, FMRIB Software Library, Oxford, UK, http://www.fmrib.ox.ac.uk/fsl). All of these maps were standardized in an MNI common space (Montreal Neurological Institute, Canada (Evans et al., 1992)) and used for subsequent post-processing analyses.

2.3. Post-processing of the imaging data: calculation of the CC volume and extraction of the CC diffusion data

An automated in-house segmentation method, executed in MATLAB (The Mathworks, Inc), was applied in each participant from individual WM probability maps, the aim being to extract the volume of CC in MNI space (Fig. 1). The callosal volume was arbitrarily defined from one midline and five para-sagittal slices (1 mm thick), resulting in one total volume of ten slices. One additional and manual step, to suppress the fornix, was realized in order to ensure an optimal segmentation, using FSL software. Then, the segmented CC was automatically subdivided into five different anteroposterior subregions according to Hofer and Frahm's parcellation (2006). To investigate audition, language and executive functions involved in schizophrenia, the regions studied were one anterior region, gathering together the CC_I (language and executive functions) and the CC_{II} (executive functions) and one posterior region, the CC_V (audition and language). Then, the individual CC mask was applied to each individual modulated probability map of WM to estimate the callosal volumes of both regions (anterior and posterior regions in cm^3). Additionally, this CC mask was applied to the different diffusion maps to extract all diffusion parameters in each participant. Loss of integrity was characterized by decreased FA (axonal degeneration) as well as increased RD/MD (demyelination) (Alexander et al., 2007; Beaulieu, 2002; Leroux et al., 2013).

2.4. Statistical analyses

To test possible differences in CC volume and integrity between the groups (HC *versus* SID *versus* LID), eight analyses of covariance (ANCOVAs, inter-group analyses) were performed with the volume and integrity data of the CC as dependent variables (volumes, FA, MD and RD in CC anterior and posterior regions) and with the groups (three levels: SID, LID and HC) as independent variables.

The results were considered significant with a $p < 0.05$. If the ANCOVA results were significant, *post-hoc* analyses were performed (Student's *t*-test). The gender was considered in these analyses as a between-subject factor since a sexual dimorphism of the CC has been described regarding the macrostructure (Ardekani et al., 2013) and the microstructure (Menzler et al., 2010). Age was also considered as a covariate since differences in age were expected between both SZ groups. Similarly, the total brain volume was considered as a covariate in the volumetric analyses as suggested in the literature on volumetric neuroimaging in schizophrenia (Ueda et al., 2010).

Spearman correlations were also performed to test relationships

Table 1
Characteristics of participants.

	Schizophrenia (SZ) groups[1] SID group (ID < 10.7 years) *n* = 21	LID group (ID ≥ 10.7 years) *n* = 22	Healthy control (HC) group *n* = 23	*p*-value
Illness duration (ID, in years)	6.6 ± 2.4 [1.3 ; 10.1]	19.2 ± 7.1 [11.7 ; 39.8]	–	< 0.0001[a,*]
Age (in years)	30.4 ± 5.3 [19.1 ; 40.4]	41.1 ± 7.9 [29.2 ; 59.8]	35.4 ± 10.3 [22.9 ; 61.6]	0.00030[#] < 0.0001[a,*] 0.047[b,*] 0.021[c,*]
Gender, Male [*n* (in%)]	12 (57.1%)	17 (77.3%)	15 (65.2%)	0.37[**]
Education level (number of years of school)	12.9 ± 2.6 [10 ; 20]	12.6 ± 2.2 [9 ; 17]	12.9 ± 1.8 [10 ; 17]	0.93[#] 0.75[a,*] 0.99[b,*] 0.73[c,*]
Medication (in chlorpromazine equivalent, mg/day)	383.7 ± 227.7 [100 ; 1000]	391.5 ± 309.2 [100 ; 1133.3]	NA	0.91[a,*]
Type of medication (%)			NA	NA
Typical	34.8	39.1		
Clozapine	30.4	26.1		
Other atypical	34.8	43.5		
Total PANSS Score	57.9 ± 15.8 [38 ; 89]	53.3 ± 10.2 [36 ; 72]	NA	0.26[a,*]
General PANSS Score	27.9 ± 6.9 [18 ; 45]	26.8 ± 4.9 [18 ; 38]		0.57[a,*]
Negative PANSS Score	17.6 ± 7.0 [8 ; 30]	14.8 ± 5.3 [9 ; 25]		0.15[a,*]
Positive PANSS Score	12.5 ± 5.4 [7 ; 24]	12.1 ± 4.4 [7 ; 21]		0.78[a,*]

Values are mean ± Standard Deviation (SD) [range] unless otherwise specified. SZ: patients with schizophrenia; SID: Short illness duration patient group; LID: Long Illness Duration patient group; HC: Healthy controls group; ID: Illness duration; *n*: number; PANSS: Positive And Negative Syndrome Scale; NA: Not Applicable;.
[1] Median of the illness duration (ID) = 10.7 years.
[#] ANOVA: Analysis of Variance;.
[*] Student's *t*-test;.
[**] χ^2 test; Significance level: $p < 0.05$.
[a] Difference between SID and LID groups;.
[b] Difference between SID and HC groups;.
[c] Difference between LID and HC groups.

between diffusion measures and volumes of the CC in each group with the integrity data as dependent variables and the volumes as independent variables according to both regions (anterior and posterior).

All statistical analyses were performed with JMP software (SAS Institute, Inc., Cary, NC, version 10.0).

3. Results

3.1. Participants

The characteristics of the three groups of participants are detailed in

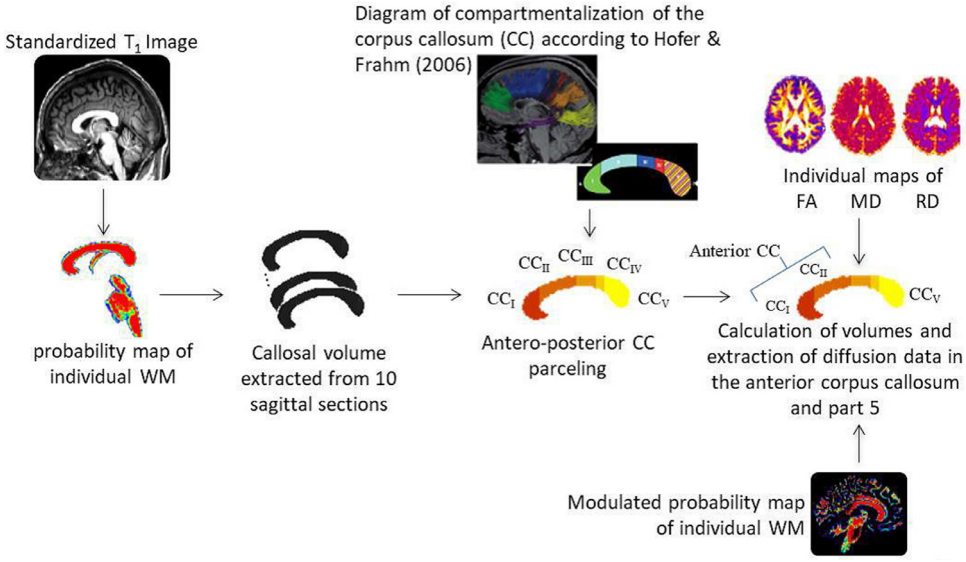

Fig. 1. Steps of post-processing allowing the calculation of the corpus callosum volumes and extraction of callosal integrity values in the regions involved in audition, language and executive functions.
CC: corpus callosum; FA: fractional anisotropy; MD: mean diffusivity; RD: radial diffusivity; WM: white matter.

Table 2
Inter-group comparisons of the corpus callosum volumes.

	SID Group $n = 21$	LID Group $n = 22$	HC Group $n = 23$	inter-group comparisons[1] p (ANCOVA)	p (*post-hoc*)
Anterior CC Volume (in cm^3)	3.07 ± 0.42 [2.28 ; 3.73]	2.87 ± 0.45 [1.81 ; 3.49]	3.12 ± 0.42 [2.48 ; 4.14]	0.045	0.041*,a 0.97*,b 0.020*,c
Posterior CC volume (in cm^3)	1.83 ± 0.32 [1.00 ; 2.40]	1.77 ± 0.33 [1.21 ; 2.36]	1.87 ± 0.21 [1.51 ; 2.13]	0.50	NA
Total Brain Volume (in cm^3)	1411.22 ± 191.90 [1146.35 ; 1694.63]	1415.20 ± 238.58 [748.45 ; 1602.54]	1440.47 ± 154.58 [1156.79 ; 1836.18]	0.87	NA

Values are mean ± Standard Deviation (SD) [range]. SID: Short illness duration patient group; LID: Long Illness Duration patient group; HC: Healthy controls group; *n*: number; NA: Not Applicable.
ANCOVA: Analysis of Covariance;.
[1] Age and total brain volume are considered as covariates and gender is considered as a between-subject factor.
* Student's *t*-test; Significance level: $p < 0.05$.
[a] Difference between SID and LID groups;.
[b] Difference between SID and HC groups;.
[c] Difference between LID and HC groups.

Table 1. The median illness duration of all SZ participants was 10.7 years. The three groups of participants included 23 HC, 21 patients with a short illness duration (mean illness duration: 6.6 years) and 22 patients with a long illness duration (mean illness duration: 19.2 years).

3.2. Volume of the corpus callosum: structural MRI data

The results concerning structural MRI data are detailed in Table 2 and in Fig. 2. ANCOVAs revealed a significant inter-group volumetric difference only in the anterior region ($p = 0.045$).

According to the *post-hoc* analyses, the LID group had significant reduction of the callosal volume in the anterior region compared to the HC group ($p = 0.020$) and to the SID group ($p = 0.041$). The SID group did not show any reduction in callosal volume in this same region compared to the HC group ($p = 0.97$).

3.3. Integrity of the corpus callosum: DTI data

The results concerning the DTI data are detailed in Table 3 and Fig. 3. ANCOVAs revealed significant inter-group microstructural differences in the anterior and posterior regions for the three diffusion parameters, except for the FA in the anterior region and MD in the posterior region (anterior FA: $p = 0.22$, posterior FA: $p = 0.0085$, anterior MD: $p = 0.012$, posterior MD: $p = 0.067$, anterior RD: $p = 0.029$, posterior RD: $p = 0.014$).

According to the *post-hoc* analyses, the LID group presented significant alterations in the callosal integrity in the anterior region (MD: $p = 0.0036$; RD: $p = 0.010$) and in the posterior region (FA: $p = 0.020$) compared to the HC group. Similarly, the SID group exhibited significant impairments in the posterior region (FA: $p = 0.0060$; RD: $p = 0.0048$) compared to the HC group. There were no significant differences between both patient groups for the three diffusion parameters in both regions.

3.4. Relationships between diffusion and volume measures of the corpus callosum in the three groups

Spearman correlations concerning relationships between diffusion and volume measures of the CC in the three groups are presented in Table 4 and revealed no significant correlation in both SZ groups. Only the HC group presented significant negative correlations in the anterior region for the MD ($r = -0.46$, $p = 0.026$) and the RD ($r = -0.56$, $p = 0.0055$), although the LID group presented close levels of correlations.

4. Discussion

To the best of our knowledge, this work is the first one that has considered both micro- and macrostructural alterations of the CC in schizophrenia according to the stage of disease. Callosal microstructural alterations were found in both SZ groups compared to the HC group but without any difference between SZ groups. Conversely, significant volumetric macrostructural alterations were detected only in the LID group compared to the HC group and to the SID group.

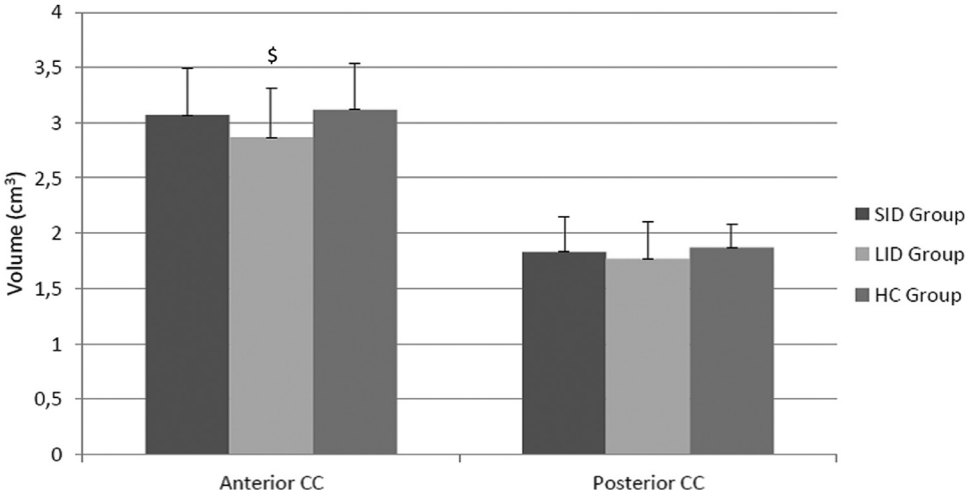

Fig. 2. Inter-group comparisons of the anterior corpus callosum volume (in cm^3).
The ANCOVAs revealed a significant inter-group volumetric difference only in the anterior region ($p = 0.045$). In *post-hoc* analyses, there was only a significant reduction of the callosal volume in the anterior region in the LID group compared to the HC group ($p = 0.020$) and the SID group ($p = 0.041$)[$].
ANCOVA: Analysis of Covariance; CC: Corpus callosum; HC: Healthy controls group; LID: Long Illness Duration patient group; SID: Short illness duration patient group. Significance level: $p < 0.05$.

Table 3
Inter-group comparisons of the callosal integrity.

Diffusion parameters	Region	SID $n = 21$	LID $n = 22$	HC $n = 23$	Inter-group comparisons[1] p (ANCOVA)	p (*post-hoc*, *t*-test)
FA (in mm^2/s)	Anterior	0.64 +/- 0.035 [0.56; 0.70]	0.62 +/- 0.028 [0.58; 0.68]	0.64 +/- 0.028 [0.57; 0.69]	0.22	NA
	Posterior	0.73 +/- 0.046 [0.60; 0.78]	0.73 +/- 0.046 [0.64; 0.84]	0.76 +/- 0.031 [0.70; 0.82]	0.0085	0.70*,a 0.0060*,b 0.020*,c
MD (in 10^{-3} mm^2/s)	Anterior	0.94 +/- 0.061 [0.85 ; 1.11]	0.97 +/- 0.047 [0.86; 1.05]	0.92 +/- 0.030 [0.86; 0.98]	0.012	0.21*,a 0.11*,b 0.0036*,c
	Posterior	0.87 +/- 0.13 [0.74; 1.30]	0.85 +/- 0.063 [0.70; 0.94]	0.81 +/- 0.037 [0.76; 0.91]	0.067	NA
RD (in 10^{-3} mm^2/s)	Anterior	0.55 +/- 0.069 [0.46; 0.75]	0.58 +/- 0.053 [0.46; 0.66]	0.53 +/- 0.036 [0.48; 0.61]	0.029	0.34*,a 0.12*,b 0.010*,c
	Posterior	0.44 +/- 0.14 [0.33; 0.89]	0.42 +/- 0.068 [0.28; 0.54]	0,36 +/- 0.039 [0.30 ; 0.46]	0.014	0.30*,a 0.0048*,b 0.090*,c

Values are mean ± Standard Deviation (SD) [range]. SID: Short illness duration patient group; LID: Long Illness Duration patient group; HC: Healthy controls group;FA: Fractional anisotropy; MD: mean diffusivity; RD: radial diffusivity; *n*: number; NA: Not Applicable;.
ANCOVA: Analysis of Covariance;.
[1] Age is considered as a covariate and gender as a between-subject factor.
* Student's *t*-test; Significance level: $p < 0.05$.
[a] Difference between SID and LID groups;.
[b] Difference between SID and HC groups;.
[c] Difference between LID and HC groups.

Among the alterations highlighted in SZ, cerebral connectivity dysfunction has led many authors to focus more specifically on WM, including the CC, which connects various brain regions (Friston, 2002; Kubicki et al., 2008). However, the macrostructural data currently available on the volume and surface of CC in SZ are much more controversial than microstructural data. Indeed, some authors found a decrease in the CC volume and/or surface in SZ groups compared to HC groups (Balevich et al., 2015; Collinson et al., 2014; Downhill et al., 2000; John et al., 2008; Knochel et al., 2012a), whereas others did not find any macrostructural difference (Chua et al., 2000; Frumin et al., 2002; Lei et al., 2015; Trehout et al., 2017; Woodruff et al., 1997). Moreover, two meta-analyses also found a decrease in the CC surface in SZ groups compared to HC groups (Arnone et al., 2008; Woodruff et al., 1995). The meta-analysis by Arnone et al. (2008) also found a CC surface decrease in a first-episode SZ subgroup compared to HC group. However, Arnone et al. (2008) included only four studies in first-episode patients and their results were in contradiction with those of Johnson et al. (2013) that showed no callosal surface difference between childhood-onset SZ and HC. Besides, Woodruff et al. (1995) did not consider the stage of disease. Regarding our results on the callosal volume, a reduction was found only in the LID group in the anterior region compared to both HC and SID groups. These results suggest that the stage of disease should be considered and that macrostructural abnormalities might only become apparent at a late stage. This finding might also explain the discrepancies from the literature that did not consider illness duration systematically. Therefore, callosal macrostructural abnormalities might be considered as an evolutionary brain marker of schizophrenia because of a late emergence of these abnormalities during the disease course.

Likewise, our microstructural results highlighted integrity loss in both SZ groups compared to the HC group in the CC anterior and posterior regions. These results support the hypothesis that microstructural alterations might be present at an early stage of the disease. In agreement with the literature, callosal microstructural abnormalities have been reported at the beginning of the disease (Zhuo et al., 2016). However, to the best of our knowledge, the callosal microstructural and macrostructural measures were both investigated in only one study and without considering the stage of disease (Rotarska-Jagiela and Linden, 2008). Moreover, few controversial studies have compared callosal microstructure between the early and late stages of disease (Kong et al., 2011; Mitelman et al., 2009). Indeed, Kong et al. (2011) identified CC microstructural abnormalities in a chronic SZ group, but not in a first-episode SZ group, compared to the HC group. They also found significant microstructural abnormalities in the chronic SZ group compared to the first-episode SZ group. Conversely, Mitelman et al. (2009) performed a longitudinal DTI study at baseline

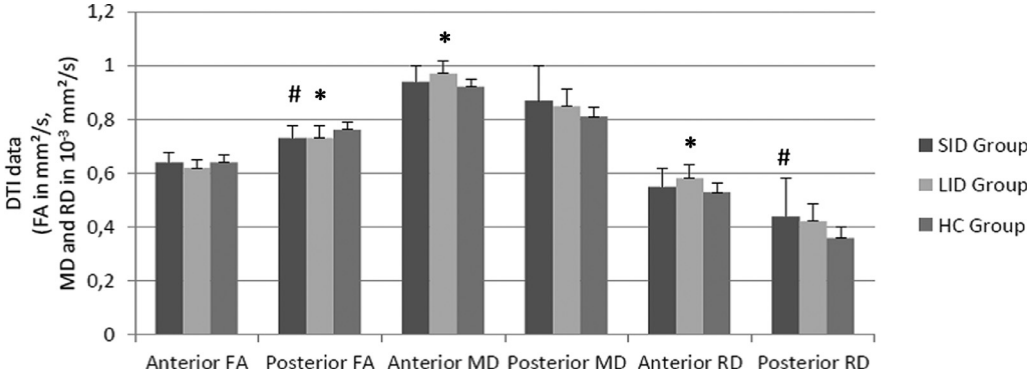

Fig. 3. Inter-group comparisons of the callosal integrity.
Significant inter-group microstructural differences were revealed by the ANCOVAs. According to the *post-hoc* analyses, the LID group presented significant alterations in the callosal integrity in the anterior region (MD: $p = 0.0036$; RD: $p = 0.010$) and in the posterior region (FA: $p = 0.020$) compared to the HC group*. Similarly, the SID group exhibited significant impairments in the posterior region (FA: $p = 0.0060$; RD: $p = 0.0048$) compared to the HC group#. There were no significant differences between both patient groups for the three diffusion parameters in both regions.
ANCOVA: Analysis of Covariance; FA: Fractional anisotropy; HC: Healthy controls group; LID: Long Illness Duration patient group; MD: mean diffusivity; RD: radial diffusivity; SID: Short illness duration patient group; Significance level: $p < 0.05$.

Table 4
Relationships between diffusion measures and volumes of the corpus callosum in the three groups (Spearman correlations).

Group	SID $n = 21$			LID $n = 22$			HC $n = 23$		
Regions\DP	FA	MD	RD	FA	MD	RD	FA	MD	RD
Anterior	0.15 (0.51)	−0.23 (0.32)	−0.18 (0.43)	0.36 (0.10)	−0.38 (0.082)	−0.42 (0.052)	0.37 (0.084)	−0.46 (0.026)	−0.56 (0.0055)
Posterior	0.18 (0.45)	−0.29 (0.20)	−0.24 (0.29)	0.10 (0.65)	−0.31 (0.16)	−0.20 (0.37)	0.11 (0.61)	−0.29 (0.18)	−0.19 (0.38)

Values are Spearman correlation coefficients (and *p*-values) between diffusion and volume data.
DP: Diffusion parameters.
n: number.
Significance level: $p < 0.05$.

and four years later in a chronic SZ group and in a matched HC group but did not show any between-group difference in the progression of callosal abnormalities. In agreement with this last study, the results of the present study did not show any significant microstructural difference between the groups of patients. Our findings showed abnormalities of callosal microstructure at the beginning of the disease without major aggravation with the evolution of the pathology. Moreover, microstructural alterations were observed in the LID group compared to the HC group in both callosal regions (anterior and posterior regions), whereas the SID group only presented a significant reduction in the posterior region. Therefore, these results suggest that the CC microstructural alterations might follow a "postero-anterior gradient" during the evolution of the disease. This gradient is also supported by the progression of the grey matter (GM) decrease in SZ during the early course of the disease (Thompson et al., 2009).

Furthermore, significant relationships between diffusion and volume measures in the anterior region were observed in the HC group but not significantly in the patient groups, although the LID group presented close correlation coefficients. These results support the fact that WM abnormalities might appear at the beginning of illness with microstructure abnormalities only. At a later stage, relationships between the CC volume and WM integrity markers might appear since macrostructure abnormalities can be also detected. Such relationships in chronic SZ patients with 12.6 years as a mean illness duration were also reported (Rotarska-Jagiela and Linden, 2008).

From a pathophysiological point of view, these results are consistent with the neurodegenerative hypothesis because of a progressive loss of WM volume in the CC, which was not visible at the beginning of the disease. The neurodegenerative models describe schizophrenia as a disease with a progressively unfavourable neurodegenerative trajectory (Kochunov and Hong, 2014). More precisely, this neurodegeneration may be characterized by an initial, rapid rate of GM loss that slows in middle life, followed by the emergence of a deficit in WM that progressively worsens with age at a constant rate (Cropley et al., 2017). Furthermore, imaging, histological, genetic and immunochemical studies support the involvement of neuroinflammatory processes in the course of schizophrenia disease progression (Pasternak et al., 2015). In SZ, a recent hypothesis assumes that neuroinflammation would trigger, but not end, in the same way as the immune response in autoimmune diseases (Najjar et al., 2013; Streit, 2006). Toxins that are released during the neuroinflammatory process may also cause collateral damage to the surrounding tissue (Whitney et al., 2009). A prolonged neuroinflammatory response in the WM may therefore damage oligodendrocytes and myelin sheath surrounding axons, thereby affecting the cerebral connectivity network (Chew et al., 2013; Deng, 2010). Inflammatory markers, including proinflammatory cytokines and chemokines, are also associated with psychosis (Chew et al., 2013). Finally, neurodegenerative and neuroinflammatory hypotheses may not be incompatible with each other. Pasternak et al. (2015) even suggested a chronologic link between them. Indeed, the early stages of schizophrenia may be more likely associated with a neuroinflammatory response rather than WM deterioration or demyelination process. In contrast, WM deterioration might play a larger role than neuroinflammation in the chronic stages of schizophrenia (Pasternak et al., 2015). In agreement with our results, CC macrostructural abnormalities may therefore be prevented by an increase in extracellular callosal volume at the beginning of the disease, and these abnormalities may be further influenced by a decline of neuroinflammatory phenomena and/or because of the late impact of the neurodegenerative process on the WM macrostructure.

This study has some limitations. Indeed, the statistical analyses conducted included 8 ANCOVAs without correction for multiple comparisons, while sample sizes were small (21 and 22 patients by group). This may lead to an inflated risk of false positive. Thus, the results of our study should be considered as “exploratory” and be cautiously interpreted. Also, antipsychotics have been implicated in structural WM differences according to the type of antipsychotic (clozapine, other atypical antipsychotics, or typical antipsychotics) (Leroux et al., 2018). Moreover, the mean illness duration of 6.6 years in the SID group did not allow us to specify the period of the illness from which the first microstructural abnormalities in schizophrenia had appeared. It may therefore be relevant to support this question by other longitudinal studies in patients with a first psychotic episode evolving into schizophrenia, as suggested by some studies (Canu et al., 2015; Zhang et al., 2016). Furthermore, another limitation of our study is the lack of age matched between groups. As expected, the SID group was indeed significantly younger than the LID group since the groups were separated from the illness duration. Likewise, the mean ages of both SZ groups were also significantly different from the HC group. Therefore, we used the age as a covariate in our statistical analyses but this precaution might remain insufficient to totally overcome the age effect across the three groups.

In conclusion, this study showed that callosal microstructural alterations were detected early in schizophrenia without any significant change thereafter, while macrostructural alterations were only detected at a later stage of the disease. Both CC micro- and macrostructural measures could be considered complementary with the first one as an early marker of WM microstructure disruption and the second one as a longer-term marker of WM abnormalities in schizophrenia. Likewise, the different stages or durations of the illness should be considered in WM micro- and macrostructural studies. The target periods of detection of both micro- and macrostructural abnormalities and the underlying pathophysiological mechanisms deserve further exploration.

Funding

This work was supported by the French Health Ministry in a “Programme Hospitalier de Recherche Clinique (PHRC)”. Funding sources were not involved in the study design, the collection, analysis and interpretation of data, the writing of the report, or the decision to submit the paper for publication.

Contributors

Drs. Jérémy Madigand, Elise Leroux and Pr. Sonia Dollfus designed the study and/or wrote the protocol. Drs. Jérémy Madigand and Elise Leroux managed the literature searches and analyses. Drs. Jérémy Madigand, Maxime Tréhout and Nicolas Delcroix undertook the post-processing of the corpus callosum, and Dr. Jérémy Madigand wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Declaration of competing interest

None to declare.

Acknowledgments

We thank Annick Razafimandimby for technical assistance and Prs. Perrine Brazo and Pascal Delamillieure for their clinical contribution.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2019.08.002.

References

Alexander, A.L., Lee, J.E., Lazar, M., Field, A.S., 2007. Diffusion tensor imaging of the brain. Neurotherapeutics 4, 316–329.
Ardekani, B.A., Figarsky, K., Sidtis, J.J., 2013. Sexual dimorphism in the human corpus callosum: an MRI study using the OASIS brain database. Cereb. Cortex. 23, 2514–2520.
Arnone, D., McIntosh, A.M., Tan, G.M., Ebmeier, K.P., 2008. Meta-analysis of magnetic resonance imaging studies of the corpus callosum in schizophrenia. Schizophr. Res. 101, 124–132.
Balevich, E.C., Haznedar, M.M., Wang, E., Newmark, R.E., Bloom, R., Schneiderman, J.S., Aronowitz, J., Tang, C.Y., Chu, K.W., Byne, W., Buchsbaum, M.S., Hazlett, E.A., 2015. Corpus callosum size and diffusion tensor anisotropy in adolescents and adults with schizophrenia. Psychiatry. Res. 231, 244–251.
Beaulieu, C., 2002. The basis of anisotropic water diffusion in the nervous system - a technical review. NMR Biomed 15, 435–455.
Canu, E., Agosta, F., Filippi, M., 2015. A selective review of structural connectivity abnormalities of schizophrenic patients at different stages of the disease. Schizophr. Res. 161, 19–28.
Cavelti, M., Winkelbeiner, S., Federspiel, A., Walther, S., Stegmayer, K., Giezendanner, S., Laimbock, K., Dierks, T., Strik, W., Horn, H., Homan, P., 2018. Formal thought disorder is related to aberrations in language-related white matter tracts in patients with schizophrenia. Psychiatry. Res. Neuroimag. 279, 40–50.
Chew, L.J., Fusar-Poli, P., Schmitz, T., 2013. Oligodendroglial alterations and the role of microglia in white matter injury: relevance to schizophrenia. Dev. Neurosci. 35, 102–129.
Chua, S.E., Sharma, T., Takei, N., Murray, R.M., Woodruff, P.W., 2000. A magnetic resonance imaging study of corpus callosum size in familial schizophrenic subjects, their relatives, and normal controls. Schizophr. Res. 41, 397–403.
Collinson, S.L., Gan, S.C., Woon, P.S., Kuswanto, C., Sum, M.Y., Yang, G.L., Lui, J.M., Sitoh, Y.Y., Nowinski, W.L., Sim, K., 2014. Corpus callosum morphology in first-episode and chronic schizophrenia: combined magnetic resonance and diffusion tensor imaging study of Chinese Singaporean patients. Br. J. Psychiatry. 204, 55–60.
Cropley, V.L., Klauser, P., Lenroot, R.K., Bruggemann, J., Sundram, S., Bousman, C., Pereira, A., Di Biase, M.A., Weickert, T.W., Weickert, C.S., Pantelis, C., Zalesky, A., 2017. Accelerated Gray and White Matter Deterioration With Age in Schizophrenia. Am. J. Psychiatry. 174, 286–295.
de, G.B., Vroomen, J., Annen, L., Masthof, E., Hodiamont, P., 2003. Audio-visual integration in schizophrenia. Schizophr. Res. 59, 211–218.
Deng, W., 2010. Neurobiology of injury to the developing brain. Nat. Rev. Neurol. 6, 328–336.
Downhill Jr., J.E., Buchsbaum, M.S., Wei, T., Spiegel-Cohen, J., Hazlett, E.A., Haznedar, M.M., Silverman, J., Siever, L.J., 2000. Shape and size of the corpus callosum in schizophrenia and schizotypal personality disorder. Schizophr. Res. 42, 193–208.
Evans, A.C., Marrett, S., Neelin, P., Collins, L., Worsley, K., Dai, W., Milot, S., Meyer, E., Bub, D., 1992. Anatomical mapping of functional activation in stereotactic coordinate space. Neuroimage 1, 43–53.
Friston, K.J., 2002. Dysfunctional connectivity in schizophrenia. World Psychiatry 1, 66–71.
Frumin, M., Golland, P., Kikinis, R., Hirayasu, Y., Salisbury, D.F., Hennen, J., Dickey, C.C., Anderson, M., Jolesz, F.A., Grimson, W.E., McCarley, R.W., Shenton, M.E., 2002. Shape differences in the corpus callosum in first-episode schizophrenia and first-episode psychotic affective disorder. Am. J. Psychiatry. 159, 866–868.
Gazzaniga, M.S., 2000. Cerebral specialization and interhemispheric communication: does the corpus callosum enable the human condition? Brain 123 (Pt 7), 1293–1326.
Hofer, S., Frahm, J., 2006. Topography of the human corpus callosum revisited–comprehensive fiber tractography using diffusion tensor magnetic resonance imaging. Neuroimage 32, 989–994.
John, J.P., Shakeel, M.K., Jain, S., 2008. Corpus callosal area differences and gender dimorphism in neuroleptic-naive, recent-onset schizophrenia and healthy control subjects. Schizophr. Res. 103, 11–21.
Johnson, S.L., Greenstein, D., Clasen, L., Miller, R., Lalonde, F., Rapoport, J., Gogtay, N., 2013. Absence of anatomic corpus callosal abnormalities in childhood-onset schizophrenia patients and healthy siblings. Psychiatry. Res. 211, 11–16.
Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13, 261–276.
Knochel, C., O'Dwyer, L., Alves, G., Reinke, B., Magerkurth, J., Rotarska-Jagiela, A., Prvulovic, D., Hampel, H., Linden, D.E., Oertel-Knochel, V., 2012a. Association between white matter fiber integrity and subclinical psychotic symptoms in schizophrenia patients and unaffected relatives. Schizophr. Res. 140, 129–135.
Knochel, C., Oertel-Knochel, V., Schonmeyer, R., Rotarska-Jagiela, A., van, d.V.V., Prvulovic, D., Haenschel, C., Uhlhaas, P., Pantel, J., Hampel, H., Linden, D.E., 2012b. Interhemispheric hypoconnectivity in schizophrenia: fiber integrity and volume differences of the corpus callosum in patients and unaffected relatives. Neuroimage 59, 926–934.
Kochunov, P., Hong, L.E., 2014. Neurodevelopmental and neurodegenerative models of schizophrenia: white matter at the center stage. Schizophr. Bull. 40, 721–728.
Kong, X., Ouyang, X., Tao, H., Liu, H., Li, L., Zhao, J., Xue, Z., Wang, F., Jiang, S., Shan, B., Liu, Z., 2011. Complementary diffusion tensor imaging study of the corpus callosum in patients with first-episode and chronic schizophrenia. J. Psychiatry. Neurosci. 36, 120–125.
Kubicki, M., Styner, M., Bouix, S., Gerig, G., Markant, D., Smith, K., Kikinis, R., McCarley, R.W., Shenton, M.E., 2008. Reduced interhemispheric connectivity in schizophrenia-tractography based segmentation of the corpus callosum. Schizophr. Res. 106, 125–131.
Lei, W., Li, N., Deng, W., Li, M., Huang, C., Ma, X., Wang, Q., Guo, W., Li, Y., Jiang, L., Zhou, Y., Hu, X., McAlonan, G.M., Li, T., 2015. White matter alterations in first episode treatment-naive patients with deficit schizophrenia: a combined VBM and DTI study. Sci. Rep. 5, 12994.
Leroux, E., Delcroix, N., Alary, M., Razafimandimby, A., Brazo, P., Delamillieure, P., Dollfus, S., 2013. Functional and white matter abnormalities in the language network in patients with schizophrenia: a combined study with diffusion tensor imaging and functional magnetic resonance imaging. Schizophr. Res. 150, 93–100.
Leroux, E., Delcroix, N., Dollfus, S., 2014. Left fronto-temporal dysconnectivity within the language network in schizophrenia: an fMRI and DTI study. Psychiatry. Res. 223, 261–267.
Leroux, E., Vandevelde, A., Trehout, M., Dollfus, S., 2018. Abnormalities of fronto-subcortical pathways in schizophrenia and the differential impacts of antipsychotic treatment: a DTI-based tractography study. Psychiatry. Res. Neuroimag. 280, 22–29.
Menzler, K., Belke, M., Wehrmann, E., Krakow, K., Lengler, U., Jansen, A., Hamer, H.M., Oertel, W.H., Rosenow, F., Knake, S., 2010. Men and women are different: diffusion tensor imaging reveals sexual dimorphism in the microstructure of the thalamus, corpus callosum and cingulum. Neuroimage 54, 2557–2562.
Mitelman, S.A., Nikiforova, Y.K., Canfield, E.L., Hazlett, E.A., Brickman, A.M., Shihabuddin, L., Buchsbaum, M.S., 2009. A longitudinal study of the corpus callosum in chronic schizophrenia. Schizophr. Res. 114, 144–153.
Najjar, S., Pearlman, D.M., Alper, K., Najjar, A., Devinsky, O., 2013. Neuroinflammation and psychiatric illness. J. Neuroinflammation 10, 43.
Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9, 97–113.
Pasternak, O., Westin, C.F., Dahlben, B., Bouix, S., Kubicki, M., 2015. The extent of diffusion MRI markers of neuroinflammation and white matter deterioration in chronic schizophrenia. Schizophr. Res. 161, 113–118.
Rotarska-Jagiela, A., Linden, D.E.J., 2008. The corpus callosum in schizophrenia_volume and connectivity changes affect specific regions. Neuroimage 39, 1522–1532.
Streit, W.J., 2006. Microglial senescence: does the brain's immune system have an expiration date? Trends. Neurosci 29, 506–510.
Thompson, P.M., Bartzokis, G., Hayashi, K.M., Klunder, A.D., Lu, P.H., Edwards, N., Hong, M.S., Yu, M., Geaga, J.A., Toga, A.W., Charles, C., Perkins, D.O., McEvoy, J., Hamer, R.M., Tohen, M., Tollefson, G.D., Lieberman, J.A., 2009. Time-lapse mapping of cortical changes in schizophrenia with different treatments. Cereb. Cortex. 19, 1107–1123.
Trehout, M., Leroux, E., Delcroix, N., Dollfus, S., 2017. Relationships between corpus callosum and language lateralization in patients with schizophrenia and bipolar disorders. Bipolar. Disord. 19, 496–504.
Ublinskii, M.V., Semenova, N.A., Lukovkina, O.V., Sidorin, S.V., Lebedeva, I.S., Akhadov, T.A., 2015. Diffusion in the corpus callosum in patients with early schizophrenia. Bull. Exp. Biol. Med. 158, 611–613.
Ueda, K., Fujiwara, H., Miyata, J., Hirao, K., Saze, T., Kawada, R., Fujimoto, S., Tanaka, Y., Sawamoto, N., Fukuyama, H., Murai, T., 2010. Investigating association of brain volumes with intracranial capacity in schizophrenia. Neuroimage 49, 2503–2508.
Vroomen, J., de, G.B., 2003. Visual motion influences the contingent auditory motion aftereffect. Psychol. Sci. 14, 357–361.
Walterfang, M., Wood, A.G., Reutens, D.C., Wood, S.J., Chen, J., Velakoulis, D., McGorry, P.D., Pantelis, C., 2008. Morphology of the corpus callosum at different stages of schizophrenia: cross-sectional study in first-episode and chronic illness. Br. J. Psychiatry. 192, 429–434.
Whitney, N.P., Eidem, T.M., Peng, H., Huang, Y., Zheng, J.C., 2009. Inflammation mediates varying effects in neurogenesis: relevance to the pathogenesis of brain injury and neurodegenerative disorders. J. Neurochem. 108, 1343–1359.

Wigand, M., Kubicki, M., Clemm von, H.C., Leicht, G., Karch, S., Eckbo, R., Pelavin, P.E., Hawley, K., Rujescu, D., Bouix, S., Shenton, M.E., Mulert, C., 2015. Auditory verbal hallucinations and the interhemispheric auditory pathway in chronic schizophrenia. World. J. Biol. Psychiatry. 16, 31–44.

Woodruff, P.W., McManus, I.C., David, A.S., 1995. Meta-analysis of corpus callosum size in schizophrenia. J. Neurol. Neurosurg. Psychiatry. 58, 457–461.

Woodruff, P.W., Phillips, M.L., Rushe, T., Wright, I.C., Murray, R.M., David, A.S., 1997. Corpus callosum size and inter-hemispheric function in schizophrenia. Schizophr. Res. 23, 189–196.

Zhang, X.Y., Fan, F.M., Chen, D.C., Tan, Y.L., Tan, S.P., Hu, K., Salas, R., Kosten, T.R., Zunta-Soares, G., Soares, J.C., 2016. Extensive white matter abnormalities and clinical symptoms in drug-naive patients with first-episode schizophrenia: a voxel-based diffusion tensor imaging study. J. Clin. Psychiatry. 77, 205–211.

Zhuo, C., Liu, M., Wang, L., Tian, H., Tang, J., 2016. Diffusion tensor MR imaging evaluation of callosal abnormalities in schizophrenia: a meta-analysis. PLoS. One. 11, e0161406.