Characteristics of the corpus callosum in chronic schizophrenia treated with clozapine or risperidone and those never-treated

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Research Article

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Abstract

Background

The corpus callosum (CC) deficits have been well documented in chronic schizophrenia. However, the long-term impacts of antipsychotic monotherapies on callosal morphology remain unclear. This cross-sectional study sought to explore micro- and macrostructural characteristics of the CC in never-treated patients and those with long-term mono-antipsychotic treatment.

Methods

The study included twenty-three clozapine-treated schizophrenia patients (CT-SCZ), 19 risperidone-treated schizophrenia patients (RT-SCZ), 23 never-treated schizophrenia patients (NT-SCZ), and 35 healthy controls (HCs). High resolution structural images and diffusion tensor imaging (DTI) data for each participant were obtained via a 3.0 T MR scanner. FreeSurfer was used to examine the volumes and fractional anisotropy (FA) values of the CC for each participant.

Results

There were significant deficits in the total and subregional CC volume, and white matter integrity in NT-SCZ in comparison with healthy subjects. Compared with NT-SCZ, both CT-SCZ and RT-SCZ showed significantly increased FA values in the anterior CC region, while only RT-SCZ showed significantly increased volume in the mid-anterior CC region. Moreover, the volume of the mid-anterior CC region was significantly smaller in CT-SCZ compared to HCs. No correlations of clinical symptoms with callosal metrics were observed.

Conclusions

Our findings provide insight into micro- and macrostructural characteristics of the CC in chronic schizophrenia patients with or without antipsychotic medications. These results suggest that chronic exposure to antipsychotic medications may have an impact on brain structure of schizophrenia patients, especially in those with risperidone treatment.

Background

The corpus callosum (CC) is the largest commissural fiber in human brain and implicated in the etiopathology of schizophrenia [1–4]. However, little is known regarding the effects of antipsychotic medications on callosal morphology in schizophrenia patients over long-term treatment [5, 6]. Compared with healthy controls, a recent study found increased volume of the posterior region of the CC in patients with long-term exposure to antipsychotic medications [5]. Moreover, patients with poor outcome after treatment had more pronounced reduction in CC size compared to good-outcome patients and healthy subjects [6]. Notably, neither of these studies included long-term drug-naive patients as a comparison group, complicating the interpretation of the findings as whether they reflect effects of neuropathology or medication remains unclear.
Prior studies have demonstrated that clozapine and risperidone may display different impacts on white matter structures in terms of their different pharmacological mechanisms [7, 8]. Clozapine, the first atypical antipsychotic, is now widely used for treatment-resistant schizophrenia in most countries [9]. It has a high affinity to dopamine D4 receptors and other receptors such as 5HT2A, 5HT1C, adrenergic receptors [10]. Risperidone is another reliable atypical antipsychotic that is antagonistic to 5HT2 and dopamine D2 receptors [10]. In contrast, clozapine has a low affinity to dopamine D2 receptors [10]. In addition, our previous study on chronic schizophrenia showed less alterations in white matter structural networks in risperidone-treated patients compared with clozapine-treated or never-treated patients [11]. However, few studies have explored the effects of long-term monotherapy with clozapine or risperidone on callosal structure in chronic schizophrenia.

In the present study, we combined structural magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) to examine the impacts of long-term clozapine and risperidone therapies on the micro- and macrostructures [fractional anisotropy (FA) & volume respectively] of the CC. In groups of never-treated and mono-antipsychotic treated chronic schizophrenia patients, FreeSurfer was used to automatically identify and segment CC for each participant to reduce random errors, rater errors and inter-participant variability of manual editing [12]. According to our previous findings [11, 13–15], we hypothesized that long-term clozapine-treated (CT-SCZ) and risperidone-treated schizophrenia patients (RT-SCZ) would show different alterations in the volume and/or FA values of the CC.

**Methods**

**Participants**

Twenty-three chronic schizophrenia patients with long-term clozapine treatment, 19 chronic schizophrenia patients with long-term risperidone treatment, 23 never-treated chronic schizophrenia patients, and 35 healthy controls (HCs) were recruited in the study. Clinical diagnoses of schizophrenia were made by an experienced psychiatrist based on the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID). The Nottingham Onset Schedule was conducted to evaluate illness onset and duration using information provided by patients, family members and available medical records [16]. The Positive and Negative Symptom Scale (PANSS) was used to estimate the severity of clinical symptoms of the patients [17].

Antipsychotic-treated patients were recruited from the local psychiatric clinic. All participants had received either clozapine or risperidone treatment consistently for over five years before entry into the study based on medical records. Never-treated patients (NT-SCZ) were recruited from a mental health screening program designed to provide psychiatric cares to individuals with serious but untreated mental illness in rural areas around the Chengdu City of China. They did not receive any antipsychotic medications due to many factors, including family stigma, the lack of understanding of the severity of mental illness, and poor socioeconomic conditions.

HCs were recruited from the same community via poster advertisements. The non-patient edition of the SCID was used to ensure lifetime absence of psychotic, anxiety and mood disorders.

Individuals with a known family history of major psychiatric illness in their first or second-degree relatives were excluded.
All participants were right-handed and met the following inclusion criteria: 1) no history of substance abuse or dependence, 2) no history of significant systemic illness, head injury or neurologic illness, and 3) no contraindication to MR scanning.

The study methods were performed in accordance with the relevant guidelines and regulations. Ethical approval for this study was approved by the research ethics committee of West China Hospital of Sichuan University. All participants provided written informed consent for study procedures, and informed consent for schizophrenia patients was obtained from their parents or legal guardians.

**MR image acquisition**

MRI examination of each subject was performed via a 3.0 T GE Signa EXCITE scanner (General Electric, Milwaukee, Wisconsin) with 8-channel phase array head coil. DTI images were obtained using a bipolar diffusion single-shot echo planar imaging sequence. Each DTI dataset included 15 images of non-collinear directions (b = 1000 s/mm$^2$) with a reference image without diffusion weighting (b = 0). The acquisition parameters were as follows: TR = 10,000 ms, TE = 70 ms, flip angle = 90°, field of view = 24 × 24 cm$^2$, matrix size = 128 × 128, number of axial slice = 50; and slice thickness = 3 mm (no gap). High resolution T1-weighted images for the purpose of registration were obtained using a three-dimensional spoiled gradient (SPGR) sequence. The acquisition parameters were as follows: TR = 8.5 ms, TE = 3.4 ms, TI = 400 ms, flip angle = 12°, field of view = 24 × 24 cm$^2$, matrix size = 256 × 256 × 128, number of axial slice = 156; and slice thickness = 1 mm (no gap).

**Imaging preprocessing and corpus callosum measurements**

The FreeSurfer software package (http://surfer.nmr.mgh.harvard.edu, version 6.0) was used to preprocess imaging data. Firstly, we conducted automated volumetric segmentation and cortical surface reconstruction of each high resolution T1-weighted data using the standard “recon-all” processing stream, as described carefully in other studies [18, 19]. Then, volumetric segmentation and cortical surface reconstruction of each participant were examined carefully in a multiple view to identify whether there were too much or not enough removed regions. Next, the “dt-recon” command was used to preprocess diffusion-weighted images based on individual anatomical data derived from the “recon-all” procedure. It was performed via an orderly process that included eddy current and motion correction employing FSL’s eddy_correct (http://www.fmrib.ox.ac.uk/fsl, version 6.0), a least squares tensor estimation using FSL’s dtit, and intra-subject registrations in native space. This yielded individual FA maps, b0 images and other relevant maps. After visually checking the registration, we resampled individual anatomical data in its’ diffusion space (b0 image) using the “mri_vol2vol” command. It output a new segmented volume named “wmparc2diff.mgz”. Lastly, the “wmparc2diff.mgz” volume of each subject was applied to the corresponding FA map to analyze white matter integrity of a special brain region.

CC was divided into five components of equal length along its primary eigendirection, corresponding to functional subdivisions, namely: anterior, mid-anterior, central, mid-posterior and posterior portions (Fig. 1) [12]. FreeSurfer was conducted to extract total and subregional volume of the CC. It was related with the lateral extent where white matter tracts that run horizontally from the mid-sagittal plane of the CC change direction bilaterally [12]. Moreover, FA values of five CC subregions were extracted according to the boundary defined by the CC volume segmentation.
Total Intracranial Volume (TIV)

We extracted total intracranial volume (TIV) (mm$^3$) of each participant in individual native space using FreeSurfer [20].

Statistical Analysis

By removing extreme outliers (individual volume or FA values greater than/less than 3 standard deviations from group mean), we applied multivariate analysis of covariance (MANCOVA) to test for between-group differences in subregional volumes and FA values of the CC. Univariate analysis of covariance (ANCOVA) was conducted to test for group differences in CC total volume. In these statistical models, diagnostic group (CT-SCZ, RT-SCZ, NC-SCHZ, HCs) and sex (females vs. males) were considered as between-subject factors, and age, years of education, TIV and daily chlorpromazine equivalent dosage were regarded as covariates[12]. Post-hoc comparisons with false discovery rate (FDR) corrections were performed once significant main effects were observed. We also examined correlations of clinical symptoms with statistically significant group differences in callosal metrics using Pearson correlation analysis. All analyses were performed using SPSS (version 18.0) and statistical significance was set at two-tailed $p < 0.05$.

Results

Demographic data

The clinical and demographic data are displayed in Table 1. Age, sex, and TIV were not significantly different among groups, though there was a significant difference in education ($P < 0.05$). PANSS total and subscale scores in NT-SCZ were significantly higher than treated patients and there was no significant difference in PANSS scores between RT-SCZ and CT-SCZ. In addition, mean daily chlorpromazine equivalent doses in RT-SCZ were significantly larger than that in CT-SCZ ($P < 0.05$).
|                          | CT-SCZ, N = 23 | RT-SCZ, N = 19 | NT-SCZ, N = 23 | HCs, N = 35 | Statistics | p value | Post-hoc analyses |
|--------------------------|----------------|----------------|----------------|-------------|------------|---------|------------------|
| Age (years)              | 48.96 ± 6.76   | 43.63 ± 7.83   | 44.26 ± 13.619| 44.29 ± 2.44| F = 2.105  | 0.105   | NS               |
| Gender (M/F)             | 14/9           | 11/8           | 12/11          | 23/22       | χ² = 0.723 | 0.868   | NS               |
| Education (years)        | 9.43 ± 2.84    | 10.58 ± 3.37   | 6.83 ± 4.78    | 8.01 ± 1.77 | F = 5.634  | 0.001*  | NT-SCZ vs. RT-SCZ:*; CT-SCZ vs. RT-SCZ:*; RT-SCZ vs. HC:* |
| Illness duration (years) | 18.34 ± 7.67   | 14.11 ± 8.43   | 16.44 ± 10.88  | -           | F = 1.114  | 0.345   | NS               |
| PANSS score              |                |                |                |             |            |         |                  |
| Total                    | 57.21 ± 11.42  | 49.44 ± 12.99  | 92.26 ± 19.53  | -           | F = 42.681 | < 0.001* | NT-SCZ vs. RT-SCZ: *; NT-SCZ vs. CT-SCZ:* |
| Positive symptoms        | 10.79 ± 3.09   | 9.61 ± 2.91    | 23.09 ± 6.61   | -           | F = 47.737 | < 0.001* | NT-SCZ vs. RT-SCZ: *; NT-SCZ vs. CT-SCZ:* |
| Negative symptoms        | 18.79 ± 5.59   | 14.83 ± 5.92   | 25.57 ± 9.59   | -           | F = 10.374 | < 0.001* | NT-SCZ vs. RT-SCZ: *; NT-SCZ vs. CT-SCZ:* |
| General psychopathological symptoms | 27.64 ± 5.32 | 24.83 ± 5.59 | 43.61 ± 8.47 | - | F = 43.858 | < 0.001* | NT-SCZ vs. RT-SCZ: *; NT-SCZ vs. CT-SCZ:* |
| Chlorpromazine equivalents (mg/day) | 233.99 ± 101.62 | 316.25 ± 115.46 | - | - | t = 2.455 | 0.019* | - |
CT-SCZ, N = 23  
Mean ± SD

RT-SCZ, N = 19  
Mean ± SD

NT-SCZ, N = 23  
Mean ± SD

HCs, N = 35  
Mean ± SD

Total Intracranial Volume (TIV) (cm³)

|                  | CT-SCZ, N = 23 | RT-SCZ, N = 19 | NT-SCZ, N = 23 | HCs, N = 35 | Statistics | p value | Post-hoc analyses |
|------------------|----------------|----------------|----------------|-------------|------------|---------|------------------|
|                  | Mean ± SD      | Mean ± SD      | Mean ± SD      | Mean ± SD   | F          |         |                  |
| Total Intracranial Volume (TIV) (cm³) | 1431.73 ± 159.18 | 1442.26 ± 175.39 | 1401.05 ± 132.88 | 1394.01 ± 224.44 | 0.401      | 0.753   | NS               |

Groups differences in callosal volumes

There were no any significant interactions between sex/age and diagnostic group for callosal volume. Univariate ANCOVA showed a significant main effect of diagnostic group on total CC volume (F = 3.701, P = 0.014). Pairwise comparison analyses revealed that NT-SCZ had significantly reduced CC volume compared to HCs (P = 0.012) (Table 2), while the other groups did not significantly differ from each other. MANCOVA of subregional volumes of the CC showed a significant main effect of diagnostic group (F = 2.465, P = 0.002), where significant differences in the volume of the mid-anterior CC region were shown among the four groups (F = 7.279, P < 0.001) (Fig. 2). Specifically, post-hoc analyses showed significantly higher mid-anterior CC volume in HCs compared with both NT-SCZ (P = 0.006) and CT-SCZ (P = 0.028). Moreover, RT-SCZ had significantly increased volume compared to NT-SCZ (P = 0.027). MANCOVA test also showed a significant difference in the volume of the central CC region among the four participant groups (F = 3.686, P = 0.015). Post-hoc analyses revealed that such difference was between HCs and NT-SCZ (P = 0.012). There were no significant group differences in the volumes of other three CC subregions.

Table 2

| Corpus callosum | CT-SCZ, N = 23 | RT-SCZ, N = 19 | NT-SCZ, N = 23 | HCs, N = 35 | F value | p value | Post-hoc analyses |
|-----------------|----------------|----------------|----------------|-------------|---------|---------|------------------|
| Anterior        | 916.73 ± 145.59 | 866.72 ± 155.71 | 831.76 ± 110.77 | 845.43 ± 124.69 | 0.875   | 0.457   | NS               |
| Mid-anterior    | 530.28 ± 135.11 | 590.23 ± 126.91 | 460.38 ± 76.92  | 611.49 ± 150.69 | 7.279   | < 0.001* | NT-SCZ vs. HCs;*; CT-SCZ vs. HCs;*; RT-SCZ vs. NT-SCZ:* |
| Central         | 546.32 ± 152.74 | 538.48 ± 123.73 | 490.27 ± 114.93 | 600.16 ± 139.44 | 3.686   | 0.015*  | NT-SCZ vs. HCs:* |
| Mid-posterior   | 479.59 ± 96.39  | 500.46 ± 107.27 | 454.47 ± 87.86  | 503.92 ± 78.22  | 1.504   | 0.219   | NS               |
| Posterior       | 942.36 ± 157.09 | 949.00 ± 172.78 | 835.62 ± 128.31 | 900.63 ± 148.86 | 2.698   | 0.050   | NS               |
| Total           | 3415.29 ± 524.04 | 3444.89 ± 553.07 | 3072.52 ± 363.73 | 3450.67 ± 414.81 | 3.701   | 0.014*  | NT-SCZ vs. HCs:* |
Groups differences in callosal FA values

FA values in the five CC subregions are listed in Table 3. No interactions of diagnostic group with sex or age for the subregional FA values were statistically different. MANCOVA test showed a significant main effect of diagnostic group (F = 2.080, P = 0.011), and there were significant differences in FA value of the anterior CC region among the four groups (F = 5.671, P = 0.001) (Fig. 3). Post-hoc analyses showed that the FA values of the anterior CC region in healthy subjects were significantly greater than that in NT-SCZ (P = 0.002), while there were no significant differences in FA value of this CC region between treated patients and HCs. In addition, both RT-SCZ and CT-SCZ had significantly increased FA values in the anterior region of the CC in contrast with NT-SCZ (P = 0.003 and P = 0.026 respectively). There were no significant group differences in FA values of other four CC subregions.

Table 3
Corpus callosum fractional anisotropy (FA) values in CT-SCZ, RT-SCZ, NT-SCZ and HCs.

| Corpus callosum | CT-SCZ, N = 23 | RT-SCZ, N = 19 Mean ± SD | NT-SCZ, N = 23 | HCs, N = 35 | F value | p value | Post-hoc analyses |
|-----------------|---------------|--------------------------|----------------|-----------|----------|----------|-------------------|
| Anterior        | 0.54 ± 0.04   | 0.57 ± 0.05              | 0.50 ± 0.06    | 0.55 ± 0.04| 5.671    | 0.001*   | NT-SCZ vs. HCs:*; CT-SCZ vs. NT-SCZ:*; RT-SCZ vs. NT-SCZ:* |
| Mid-anterior    | 0.43 ± 0.06   | 0.42 ± 0.04              | 0.43 ± 0.05    | 0.42 ± 0.04| 0.610    | 0.610    | NS                |
| Central         | 0.45 ± 0.08   | 0.45 ± 0.06              | 0.47 ± 0.05    | 0.47 ± 0.06| 0.804    | 0.495    | NS                |
| Mid-posterior   | 0.41 ± 0.07   | 0.42 ± 0.07              | 0.42 ± 0.06    | 0.41 ± 0.04| 0.084    | 0.969    | NS                |
| Posterior       | 0.60 ± 0.05   | 0.64 ± 0.06              | 0.63 ± 0.06    | 0.63 ± 0.04| 1.290    | 0.283    | NS                |

Relationships with clinical symptoms

The volumes of the mid-anterior CC region and the FA values of the anterior CC region in patients were not significantly associated with PANSS total or subscale scores.

Discussion

To the best of our knowledge, this is the first study to date investigating the impact of long-term monotherapy of clozapine and risperidone on callosal structure in chronic schizophrenia. Our analyses demonstrated significant deficits of micro- and macrostructure of the CC in never-treated patients that were mainly located in anterior and mid-anterior CC. Moreover, patients receiving antipsychotic medications showed significantly increased FA values in the anterior CC region in comparison with NT-SCZ, and only patients with risperidone treatment had larger volume in the mid-anterior CC region compared with NT-SCZ. Together, these findings
suggest that chronic exposure to clozapine and risperidone may have different effects on callosal structure in schizophrenia.

The findings of our present study agree well with other studies in the literature demonstrating that chronic patients were associated with smaller CC volume or FA value in comparison with healthy comparison subjects [3, 12, 21–23]. As an extension of prior findings, one important observation here is that callosal deficits were mainly located in anterior and mid-anterior CC. White matter fibers passing through these subregions are responsible for connecting the frontal lobes [24, 25]. Therefore, anatomical alterations in the anterior and mid-anterior region of the CC may be related to structural and functional abnormalities of the frontal lobe in schizophrenia, which generate delusions and hallucinations [26, 27]. However, other studies showed that chronic schizophrenia patients had more widespread deficits that were located in both anterior and posterior region of the CC [3, 21, 22]. This discrepancy may be due to sample heterogeneities related to race, handedness, sex, and age, and to methodological differences [3]. Apart from anterior and mid-anterior CC, we also observed significant volume reduction in central CC in patients, which is in line with findings from Collinson et al [12]. Notably, dynamical alterations of this subregion in schizophrenia are associated with stage of illness [12]. Thus, it is interesting to explore whether structural alterations in central CC are a stable biomarker to predict the developmental trajectory of schizophrenia in future studies.

The observation that micro- and macrostructural abnormalities of the CC in schizophrenia were located in different subregions is in line with several previous studies [21, 26]. Here, we found that alterations of callosal volume were in the mid-anterior and central region, and abnormalities of white matter integrity were only in the anterior region of the CC. It has been proposed that changes in the number of axons and the degree of myelination may lead to the changes in white matter volume but not anisotropy [12, 28, 29]. Since the index of anisotropy is related with fiber integrity [30, 31], its change in schizophrenia patients may relate to disruptions of oligodendrocytes and/or myelin surrounding axons because of inflammation or dysregulations of neuroinflammatory responses [32–35]. Our findings suggest different pathophysiological processes in these subregions of the CC.

The current findings, together with findings from previous studies, suggest that chronic exposure to antipsychotics may have an impact on anatomical organization of the CC in schizophrenia [15, 36]. In this study, both CT-SCZ and RT-SCZ showed significantly increased FA values in the anterior CC region in comparison with NT-SCZ. A series of studies have demonstrated that antipsychotic medications, such as clozapine and risperidone, may modulate inflammations and immune responses through reduced activation of microglia and macrophages, increased level of anti-inflammatory cytokines, and inhibition of the release of proinflammatory cytokines [37–39]. Therefore, clozapine and risperidone may repair white matter microstructures of the CC by reducing inflammation or immune responses. Interestingly, only patients receiving long-term risperidone, not clozapine, showed significantly increased volume of mid-anterior CC. It has been suggested that dopamine D2 receptor signal pathway may indirectly activate Akt and glycogen synthase kinase 3 (GSK3) to inhibit myelination by regulating a β-arresting 2 (βArr2)/protein phosphatase 2A (PP2A) signaling complex [40]. Evidences from gene expression profiling and neuroimaging studies also support the hypothesis that dysregulation of the dopaminergic system in psychiatric disorders is associated with aberrant dopamine receptor signaling on oligodendrocytes, further leading to myelination impairment [40, 41]. Bartzokis et al found that typical and atypical antipsychotics differently mitigated myelination deficits in schizophrenia.
depending on their affinities to dopamine D2 receptors [8, 42, 43]. Since risperidone has a stronger affinity for dopamine D2 receptors than clozapine [10], our findings may suggest that different impacts of two drugs on CC are related to their different abilities in modulating the dopaminergic system.

There are several limitations in the present study. First, because that this study is a cross-sectional design and it lack of random assignments to different antipsychotic medications for schizophrenia patients, it should be careful to interpret our current findings. However, it is unethical and challenging to request the patients to receive a single antipsychotic treatment for over five years in a longitudinal study with a randomize design. Therefore, our cross-sectional design may be a feasible method to explore the effects of long-term usage of antipsychotic medications on human brain. Second, the sample size in this study is relatively small, and may be not completely representative. Third, the usage of non-antipsychotic medications was not controlled according to individual clinical condition.

Conclusions

Using comparing schizophrenia patients with long-term mono-antipsychotic medications with unmedicated chronic patients and healthy subjects, the present study demonstrates differential alterations of callosal structure in patients with different antipsychotic treatments. These findings suggest that chronic exposure to antipsychotic medications may have an impact on brain structure of schizophrenia patients, especially in those with risperidone treatment.

Declarations

Ethics approval and consent to participate

The study methods were performed in accordance with the relevant guidelines and regulations. Ethical approval for this study was approved by the research ethics committee of West China Hospital of Sichuan University. All participants provided written informed consent for study procedures, and informed consent for schizophrenia patients was obtained from their parents or legal guardians.

Availability of data and materials

The datasets in the current study are not publicly available due to their containing information that could compromise patients’ privacy.

Competing interests

Dr. Zhang consults to VeraSci. Other authors declare no conflicts of interest in relation to the subject of this study.

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Authors' contributions

Su Lui contributed to the conception and design of the study. Bo Tao, Yuan Xiao, Wenjing Zhang and Chengmin Yang contributed to the acquisition, or analysis and interpretation of data. Bo Tao, Yuan Xiao, Hengyi Cao, Qiyong Gong and Su Lui contributed to the drafting of the manuscript, while all authors made critical revision of the manuscript for important intellectual content and gave final approval of the version to be published.

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Abbreviations

ANCOVA: analysis of covariance, CC: corpus callosum, CT-SCZ: clozapine-treated schizophrenia patients, DTI: diffusion tensor imaging, FA: fractional anisotropy, FDR: false discovery rate, GSK: glycogen synthase kinase 3, HCs: healthy controls, MANCOVA: multivariate analysis of covariance, MRI: magnetic resonance imaging, NT-SCZ: never-treated schizophrenia patients, PANSS: Positive and Negative Symptom Scale, RT-SCZ: risperidone-treated schizophrenia patients, TIV: total intracranial volume.

References

1. Walterfang M, Velakoulis D: Callosal morphology in schizophrenia: what can shape tell us about function and illness? Br J Psychiatry 2014, 204(1):9-11.
2. Shahab S, Stefanik L, Foussias G, Lai MC, Anderson KK, Voineskos AN: Sex and Diffusion Tensor Imaging of White Matter in Schizophrenia: A Systematic Review Plus Meta-analysis of the Corpus Callosum. Schizophr Bull 2018, 44(1):203-221.
3. Zhuo C, Liu M, Wang L, Tian H, Tang J: Diffusion Tensor MR Imaging Evaluation of Callosal Abnormalities in Schizophrenia: A Meta-Analysis. PLoS One 2016, 11(8):e0161406.
4. Arnone D, McIntosh AM, Tan GM, Ebmeier KP: Meta-analysis of magnetic resonance imaging studies of the corpus callosum in schizophrenia. Schizophr Res 2008, 101(1-3):124-132.
5. de Moura MTM, Zanetti MV, Duran FLS, Schaufelberger MS, Menezes PR, Scanzufca M, Busatto GF, Serpa MH: Corpus callosum volumes in the 5 years following the first-episode of schizophrenia: Effects of antipsychotics, chronicity and maturation. Neuroimage Clin 2018, 18:932-942.
6. Mitelman SA, Nikiforova YK, Canfield EL, Hazlett EA, Brickman AM, Shihabuddin L, Buchsbaum MS: A longitudinal study of the corpus callosum in chronic schizophrenia. Schizophr Res 2009, 114(1-3):144-153.
7. Leroux E, Vandeveld A, Trehout M, Dollfus S: Abnormalities of fronto-subcortical pathways in schizophrenia and the differential impacts of antipsychotic treatment: a DTI-based tractography study. Psychiatry Res Neuroimaging 2018, 280:22-29.

8. Bartzokis G, Lu PH, Stewart SB, Oluwadara B, Lucas AJ, Pantages J, Pratt E, Sherin JE, Altsheuler LL, Mintz J et al.: In vivo evidence of differential impact of typical and atypical antipsychotics on intracortical myelin in adults with schizophrenia. Schizophr Res 2009, 113(2-3):322-331.

9. Howes OD, McCutcheon R, Agid O, de Bartolomeis A, van Beveren NJ, Birnbaum ML, Bloomfield MA, Bressan RA, Buchanan RW, Carpenter WT et al.: Treatment-Resistant Schizophrenia: Treatment Response and Resistance in Psychosis (TRRIP) Working Group Consensus Guidelines on Diagnosis and Terminology. Am J Psychiatry 2017, 174(3):216-229.

10. Tsermpini EE, Assimakopoulos K, Bartsakoulia M, Ionomon G, Papadima EM, Mitropoulos K, Squassina A, Patrinos GP: Individualizing clozapine and risperidone treatment for schizophrenia patients. Pharmacogenomics 2014, 15(1):95-110.

11. Luo C, Lencer R, Hu N, Xiao Y, Zhang W, Li S, Lui S, Gong Q: Characteristics of white matter structural networks in chronic schizophrenia treated with clozapine or risperidone and those never-treated. Int J Neuropsychopharmacol 2020.

12. Collinson SL, Gan SC, Woon PS, Kuswanto C, Sum MY, Yang GL, Lui JM, Sitoh YY, Nowinski WL, Sim K: Corpus callosum morphology in first-episode and chronic schizophrenia: combined magnetic resonance imaging and diffusion tensor imaging study of Chinese Singaporean patients. Br J Psychiatry 2014, 204(1):55-60.

13. Liu N, Xiao Y, Zhang W, Tang B, Zeng J, Hu N, Chandan S, Gong Q, Lui S: Characteristics of gray matter alterations in never-treated and treated chronic schizophrenia patients. Transl Psychiatry 2020, 10(1):136.

14. Yao L, Li F, Liu J, Liao W, Li X, Li M, Meng Y, Liang S, Zhang C, Yang X et al.: Functional brain networks in never-treated and treated long-term Ill schizophrenia patients. Neuropsychopharmacology 2019, 44(11):1940-1947.

15. Xiao Y, Sun H, Shi S, Jiang D, Tao B, Zhao Y, Zhang W, Gong Q, Sweeney JA, Lui S: White Matter Abnormalities in Never-Treated Patients With Long-Term Schizophrenia. Am J Psychiatry 2018, 175(11):1129-1136.

16. Singh SP, Cooper JE, Fisher HL, Tarrant CJ, Lloyd T, Banjo J, Corfe S, Jones P: Determining the chronology and components of psychosis onset: The Nottingham Onset Schedule (NOS). Schizophr Res 2005, 80(1):117-130.

17. Kay SR, Opler LA, Lindenmayer JP: Reliability and validity of the positive and negative syndrome scale for schizophrenics. Psychiatry Res 1988, 23(1):99-110.

18. Zhang W, Deng W, Yao L, Xiao Y, Li F, Liu J, Sweeney JA, Lui S, Gong Q: Brain Structural Abnormalities in a Group of Never-Medicated Patients With Long-Term Schizophrenia. Am J Psychiatry 2015, 172(10):995-1003.

19. Segonne F, Dale AM, Busa E, Glessner M, Salat D, Hahn HK, Fischl B: A hybrid approach to the skull stripping problem in MRI. Neuroimage 2004, 22(3):1060-1075.

20. Buckner RL, Head D, Parker J, Fotenos AF, Marcus D, Morris JC, Snyder AZ: A unified approach for morphometric and functional data analysis in young, old, and demented adults using automated atlas-
based head size normalization: reliability and validation against manual measurement of total intracranial volume. Neuroimage 2004, 23(2):724-738.

21. Madigand J, Trehout M, Delcroix N, Dollfus S, Leroux E: Corpus callosum microstructural and macrostructural abnormalities in schizophrenia according to the stage of disease. Psychiatry Res Neuroimaging 2019, 291:63-70.

22. Friedman JI, Tang C, Carpenter D, Buchsbaum M, Schmeidler J, Flanagan L, Golembo S, Kanellopoulou I, Ng J, Hof PR et al: Diffusion tensor imaging findings in first-episode and chronic schizophrenia patients. Am J Psychiatry 2008, 165(8):1024-1032.

23. Kubicki M, Park H, Westin CF, Nestor PG, Mulkern RV, Maier SE, Niznikiewicz M, Connor EE, Levitt JJ, Frumin M et al: DTI and MTR abnormalities in schizophrenia: Analysis of white matter integrity. Neuroimage 2005, 26(4):1109-1118.

24. Lee BY, Zhu XH, Li X, Chen W: High-resolution imaging of distinct human corpus callosum microstructure and topography of structural connectivity to cortices at high field. Brain Struct Funct 2019, 224(2):949-960.

25. Hofer S, Frahm J: Topography of the human corpus callosum revisited–comprehensive fiber tractography using diffusion tensor magnetic resonance imaging. Neuroimage 2006, 32(3):989-994.

26. Knöchel C, Oertel-Knöchel V, Schönmeyer R, Rotarska-Jagiela A, van de Ven V, Prvulovic D, Haenschel C, Uhlhaas P, Pantel J, Hampel H et al: Interhemispheric hypoconnectivity in schizophrenia: Fiber integrity and volume differences of the corpus callosum in patients and unaffected relatives. NeuroImage 2012, 59(2):926-934.

27. Jardri R, Pouchet A, Pins D, Thomas P: Cortical activations during auditory verbal hallucinations in schizophrenia: a coordinate-based meta-analysis. Am J Psychiatry 2011, 168(1):73-81.

28. Hugenschmidt CE, Peiffer AM, Kraft RA, Casanova R, Deibler AR, Burdette JH, Maldjian JA, Laurienti PJ: Relating imaging indices of white matter integrity and volume in healthy older adults. Cereb Cortex 2008, 18(2):433-442.

29. Cercignani M, Horsfield MA: The physical basis of diffusion-weighted MRI. Journal of the neurological sciences 2001, 186 Suppl 1:S11-14.

30. Alexander AL, Lee JE, Lazar M, Field AS: Diffusion tensor imaging of the brain. Neurotherapeutics : the journal of the American Society for Experimental NeuroTherapeutics 2007, 4(3):316-329.

31. Le Bihan D, Mangin JF, Poupon C, Clark CA, Pappata S, Molko N, Chabriat H: Diffusion tensor imaging: concepts and applications. J Magn Reson Imaging 2001, 13(4):534-546.

32. Fu G, Zhang W, Dai J, Liu J, Li F, Wu D, Xiao Y, Shah C, Sweeney JA, Wu M et al: Increased Peripheral Interleukin 10 Relate to White Matter Integrity in Schizophrenia. Frontiers in Neuroscience 2019, 13.

33. Najjar S, Pearlman DM: Neuroinflammation and white matter pathology in schizophrenia: systematic review. Schizophr Res 2015, 161(1):102-112.

34. Chew L-J, Fusar-Poli P, Schmitz T: Oligodendroglial Alterations and the Role of Microglia in White Matter Injury: Relevance to Schizophrenia. Developmental Neuroscience 2013, 35(2-3):102-129.

35. Fillman SG, Cloonan N, Catts VS, Miller LC, Wong J, McCrossin T, Cairns M, Weickert CS: Increased inflammatory markers identified in the dorsolateral prefrontal cortex of individuals with schizophrenia. Mol Psychiatry 2013, 18(2):206-214.
36. Yang C, Zhang W, Yao L, Liu N, Shah C, Zeng J, Yang Z, Gong Q, Lui S: Functional Alterations of White Matter in Chronic Never-Treated and Treated Schizophrenia Patients. J Magn Reson Imaging 2020, 52(3):752-763.

37. Giridharan VV, Scaini G, Colpo GD, Doifode T, Pinjari OF, Teixeira AL, Petronilho F, Macedo D, Quevedo J, Barichello T: Clozapine Prevents Poly (I:C) Induced Inflammation by Modulating NLRP3 Pathway in Microglial Cells. Cells 2020, 9(3).

38. Crocker CE, Tibbo PG: Confused Connections? Targeting White Matter to Address Treatment Resistant Schizophrenia. Front Pharmacol 2018, 9:1172.

39. O’Sullivan D, Green L, Stone S, Zareie P, Kharkrang M, Fong D, Connor B, La Flamme AC: Treatment with the antipsychotic agent, risperidone, reduces disease severity in experimental autoimmune encephalomyelitis. PLoS One 2014, 9(8):e104430.

40. Bartzokis G: Neuroglialpharmacology: myelination as a shared mechanism of action of psychotropic treatments. Neuropharmacology 2012, 62(7):2137-2153.

41. Feng Y: Convergence and divergence in the etiology of myelin impairment in psychiatric disorders and drug addiction. Neurochem Res 2008, 33(10):1940-1949.

42. Bartzokis G, Lu PH, Amar CP, Raven EP, Detore NR, Altshuler LL, Mintz J, Ventura J, Casaus LR, Luo JS et al: Long acting injection versus oral risperidone in first-episode schizophrenia: differential impact on white matter myelination trajectory. Schizophr Res 2011, 132(1):35-41.

43. Bartzokis G, Lu PH, Nuechterlein KH, Gitlin M, Doi C, Edwards N, Lieu C, Altshuler LL, Mintz J: Differential effects of typical and atypical antipsychotics on brain myelination in schizophrenia. Schizophr Res 2007, 93(1-3):13-22.

Figures
Figure 1

Corpus callosum was divided into five components of equal length along its’ primary eigendirection, corresponding to functional subdivisions, namely: anterior, mid-anterior, central, mid-posterior and posterior portions Note: A, anterior (rostrum); MA, mid-anterior (genu); C, central (truncus/body); MP, mid-posterior (anterior splenium); P, posterior (posterior splenium).
Figure 2

Volume (mm$^3$) of the mid-anterior CC region in CT-SCZ, RT-SCZ, NT-SCZ and HCs Note: CT-SCZ, clozapine-treated schizophrenia patients; RT-SCZ, risperidone-treated schizophrenia patients; NT-SCZ, never-treated schizophrenia patients; HCs, healthy controls; CC, corpus callosum; *, $P < 0.05$. 
Figure 3

Fractional anisotropy (FA) of the anterior CC region in CT-SCZ, RT-SCZ, NT-SCZ and HCs Note: CT-SCZ, clozapine-treated schizophrenia patients; RT-SCZ, risperidone-treated schizophrenia patients; NT-SCZ, never-treated schizophrenia patients; HCs, healthy controls; CC, corpus callosum; *, P < 0.05.