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Is treatment-resistant schizophrenia associated with distinct neurobiological callosal connectivity abnormalities?

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Abstract

Background. Resistance to antipsychotic treatment affects up to 30% of patients with schizophrenia. Although the time course of development of treatment-resistant schizophrenia (TRS) varies from patient to patient, the reasons for these variations remain unknown. Growing evidence suggests brain dysconnectivity as a significant feature of schizophrenia. In this study, we compared fractional anisotropy (FA) of brain white matter between TRS and non–treatment-resistant schizophrenia (non-TRS) patients. Our central hypothesis was that TRS is associated with reduced FA values.

Methods. TRS was defined as the persistence of moderate to severe symptoms after adequate treatment with at least two antipsychotics from different classes. Diffusion-tensor brain MRI obtained images from 34 TRS participants and 51 non-TRS. Whole-brain analysis of FA and axial, radial, and mean diffusivity were performed using Tract-Based Spatial Statistics (TBSS) and FMRIB's Software Library (FSL), yielding a contrast between TRS and non-TRS patients, corrected for multiple comparisons using family-wise error (FWE) < 0.05.

Results. We found a significant reduction in FA in the splenium of corpus callosum (CC) in TRS when compared to non-TRS. The antipsychotic dose did not relate to the splenium CC.

Conclusion. Our results suggest that the focal abnormality of CC may be a potential biomarker of TRS.

Introduction

Schizophrenia is a heterogeneous disease comprising positive symptoms, such as delusions and hallucinations; negative symptoms, such as avolition and social withdrawal; cognitive impairment; and mood dysregulation. While antipsychotic medication is the mainstay of treatment for this condition, it is ineffective for approximately 30% of patients. Treatment-resistant schizophrenia (TRS) is defined as the failure to respond to at least two antipsychotic drug trials administered at an adequate dose for an appropriate period of time.[1] Resistance to treatment may cause significant personal, family, and social difficulties, resulting in increased hospitalization rates, longer hospital stays, and the significant consumption of other resources.[2,3] These manifold consequences underscore the need for effective therapeutic intervention.

Several lines of evidence indicate that TRS may be a distinct subtype of schizophrenia with different neurochemical abnormalities. This hypothesis is inferred by the observations that responders to treatment present more pronounced dopaminergic abnormalities, while nonresponders present dysfunction in the glutamatergic system.[4,5] Also, clozapine, an atypical antipsychotic with weak dopamine antagonism,[6] remains the reference standard treatment for TRS.[7,8]

White matter (WM) studies[9–12] have reported abnormalities supporting the hypothesis of dysconnectivity in schizophrenia. The effect of antipsychotics on myelin is not well established. Bartzokis et al[13] suggested that the choice of antipsychotics may impact the myelination of posterior intracortical circuits in adults with schizophrenia. Other research suggests that

antipsychotics increase intracortical myelin early in the course of their administration.[14,15] Garver et al[16] demonstrated that an antipsychotic-induced cascade might partially restore myelin integrity and concomitant functional connectivity in TRS patients.

Understanding of the myelinated fibers connecting cortical and subcortical grey matter (GM) has advanced with the advent of magnetic resonance diffusion tensor imaging (DTI).[17] This can detect changes in WM fiber systems even in the absence of macrostructural changes.[18,19] One comparison of patients with TRS to healthy controls found the former to have reduced fractional anisotropy (FA) and increased radial diffusivity (RD) in the genu, body, and splenium of the corpus callosum (CC), the right posterior limb of the internal capsule, the right external capsule, and the right temporal inferior longitudinal fasciculus.[20]

However, few neuroimaging studies have considered differences between individuals with TRS and those with non-TRS. It thus remains unclear whether the neurobiological profiles of these two populations are distinct. In the present study, we compared microstructural abnormalities in the fiber tracts between TRS and non-TRS. We hypothesized that reduction in FA values in TRS would be greater than in non-TRS.

Materials and methods

Subjects

This study recruited a cross-sectional sample of multiepisode patients with TRS (n = 34) and non-TRS (n = 51) from the outpatient Schizophrenia Program (PROESQ) of the Universidade Federal de São Paulo (São Paulo, Brazil) between 2011 and 2015. Inclusion criteria were as follows: (1) a research interview confirming the diagnosis of schizophrenia according to the DSM-IV (American Psychiatric Association, 1994), (2) age between 16 and 60 years, (3) no neurological disease, (4) no severe intellectual disability, and (5) no comorbidity with other axis I disorders. The Research Ethics Committee approved the study of the Federal University of São Paulo (UNIFESP) (protocol numbers 0661/11 and 1737/06). All participants or their caregivers provided written informed consent prior to inclusion.

Structured diagnostic and symptom evaluation

The diagnosis was confirmed using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I).[21] The Positive and Negative Syndrome Scale (PANSS) was administered to all patients to evaluate psychopathology. Sociodemographic information and medical histories were collected from the patients and confirmed by their relatives or caregivers.

Outpatient sample: clinical assessment and resistance to treatment

The outpatients were assessed by four independent trained raters who were regular members of the medical staff and participated in routine clinical decisions. Response to previous antipsychotics was determined by a consensus of at least two experienced clinicians in routine meetings. Diagnosis of TRS followed the criteria established by the International Psychopharmacology Algorithm Project (IPAP): (1) persistence of symptoms after at least two antipsychotics administered for at least 4 weeks, each at doses equivalent to chlorpromazine 400 mg/d or risperidone 5 mg/d; (2) persistence of at least two symptoms of moderate or greater severity; or at least one symptom with at least a severe rating among the following PANSS items: delusions (P1), conceptual disorganization (P2), hallucinatory behavior (P3), or suspiciousness (P6). Additional information on antipsychotic treatment was collected from the patients' medical records and other staff members. Information about treatment adherence was obtained from caregivers, staff members, and medical records.

MRI data acquisition

All brain scans were obtained at the Department of Diagnostic Radiology (UNIFESP) on a 1.5 T Siemens scanner (Magnetom Sonata AG, Medical Solutions, Erlangen, Germany) with an eight-channel head coil (MAGNETON Sonata). For each patient, diffusion-weighted images of the whole brain in the axial orientation were obtained according to the following parameters: FOV = 256 mm, 50 slices, 128 × 128 matrix, TR = 7000 ms, TE = 85 ms, b-value = 1000 s/mm^2, slice thickness = 3.0 mm, and 12 noncollinear diffusion directions.

Image analysis

Data were preprocessed following the basic pipeline available on FMRIB's Software Library (FSL) (www.fmrib.ox.ac.uk/fsl).[22] All images were corrected for eddy currents using FMRIB's Diffusion Toolbox (FDT). Skull stripping was then performed by Brain Extraction Toolbox (BET). Diffusion tensors were subsequently fitted for each voxel (using the DTIFIT tool) to calculate the FA, RD, axial diffusivity (AD), and mean diffusivity (MD) maps.

Whole-brain voxel-wise cross-subject analyses were performed using Tract-Based Spatial Statistics (TBSS).[23] All FA maps were nonlinearly registered to a Montreal Neurological Institute (MNI) standard space target image and were used to create an average skeleton, and the FA maps of each subject were then projected onto a standard mean FA skeleton at a threshold of 0.2. The same procedure was repeated for the RD, AD, and MD maps.

We then performed the automated extraction of the mean FA value from all regions. This extraction was based on the Johns Hopkins University atlas of WM tractography[24,25] and the atlas published by the International Consortium of Brain Mapping (ICBM) DTI-81.[26]

Statistical analyses

A threshold-free cluster enhancement (TFCE) approach was used for statistical analyses to identify the main effect of the groups (TRS vs non-TRS).

We performed a TFCE by applying 10 000 permutations on unsmoothed statistical maps using the Randomize tool.[27] The level of significance corrected for the family-wise error (FWE) rate was set to $P < .05$. To identify potential confounding effects, we included the factors of age and sex in the GLM matrix. The voxel-wise statistical significance level corrected for the FWE was set to $P < .05$. The same procedure was used to assess the RD, AD, and MD maps. The tool cluster of the FSLv6.0[28] was used to report cluster information.

To identify differences in demographic and clinical characteristics, we used SPSS 23.0 to perform one-way ANOVA or chi-square tests (Table 1). The level of significance was set to $P < .05$.

A stepwise, confirmatory multivariate analysis of FA values extracted from regions of interest was performed to investigate the effect of the relationship between antipsychotic dose and the regions of interest found in the exploratory analysis with SPSS 23.0. Sex, age, duration of illness, antipsychotic dose (chlorpromazine

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dose equivalent), and the PANSS positive and negative scores were used as independent variables. The FA scores of the splenium of the CC was used as the dependent variable.

Results

The demographic characteristics of the participants are shown in Table 1. Patients with TRS and non-TRS did not differ in age, sex, duration of illness, or the age of onset. However, individuals with TRS were more symptomatic across all symptom domains. All TRS patients were receiving clozapine. Non-TRS individuals received the following antipsychotics: olanzapine (59.2%), risperidone (16.3%), aripiprazole (8.2%), quetiapine (8.2%), chlorpromazine (2.0%), haloperidol (2.0%), and long-acting risperidone (2.0%).

Whole-brain analysis in TBSS

The whole-brain analysis in TBSS showed that in TRS patients, there were a significant FA reduction in the splenium of the CC than did non-TRS ($P < .05$, FWE corrected; cluster size, 8825; location of maximum z score [x, y, z], −19, −34, 32; Figure 1). There was no increased FA in TRS compared with non-TRS. No differences were found between the two populations in other DTI measures (RD, AD, MD).

Table 1. Sociodemographic and Clinical Characteristics

	TRS Patients (n = 34)	non-TRS Patients (n = 51)	*P* value
Age (mean/SD) years	37.42/8.61	36.75/10.85	.830
Sex (male %)	64.7	70.6	.023
Duration of illness (mean/SD) years	15.5/7.47	14.3/8.85	.437
Age of onset (mean/SD) years	22.2/6.63	24.1/5.89	.123
PANSS positive (mean/SD)	14.52/4.74	11.63/3.91	.002
PANSS negative (mean/SD)	18.88/5.53	16.47/5.03	.004
PANSS general (mean/SD)	31.94/8.23	27.67/7.08	.006
PANSS total (mean/SD)	65.59/15.55	55.98/12.80	.001

Abbreviations: PANSS, Positive and Negative Syndrome Scale; SD, standard deviation.

Confirmatory analysis

We found no relationship between antipsychotic dose and the FA scores of splenium of the CC.

Discussion

Our results partially confirm our major hypothesis: TRS patients present a significantly lower FA in the splenium of the CC relative to non-TRS patients. However, no differences in RD, AD, or MD maps were found.

Reduced FA in the splenium of the CC seems to be the most consistent finding in the schizophrenia literature to date.[29–31] Decreases in FA could be attributed to lower myelination, neuronal fiber density, or directional coherence.[32] Few neuroimaging studies have compared TRS to non-TRS. However, as the main interhemispheric commissure of WM, aberrations in the CC causing abnormal interhemispheric connectivity have been implicated in the neuropathophysiology of schizophrenia and could be central in TRS.[31] Anomalies have been reported in the CCs of patients with TRS relative to healthy controls.[20,33] However, while a meta-analysis of 15 studies found that patients with TRS presented significant FA reductions in their CCs relative to healthy controls, this finding was inconsistent across the investigations considered.[34] While a DTI whole-brain analysis has also revealed decreased FA values in the CCs of patients with TRS,[20,35,36] none were found in other studies.[37]

RD increases in the CC have also been observed in patients with TRS relative to healthy controls, suggesting that patients with schizophrenia exhibit deficits in microstructural organization.[20] Kochunov and collaborators found a pattern of regional WM deficit in schizophrenia that was significantly associated with resistance to treatment, suggesting that the extent of regional WM vulnerability can already be observed in schizophrenia since the

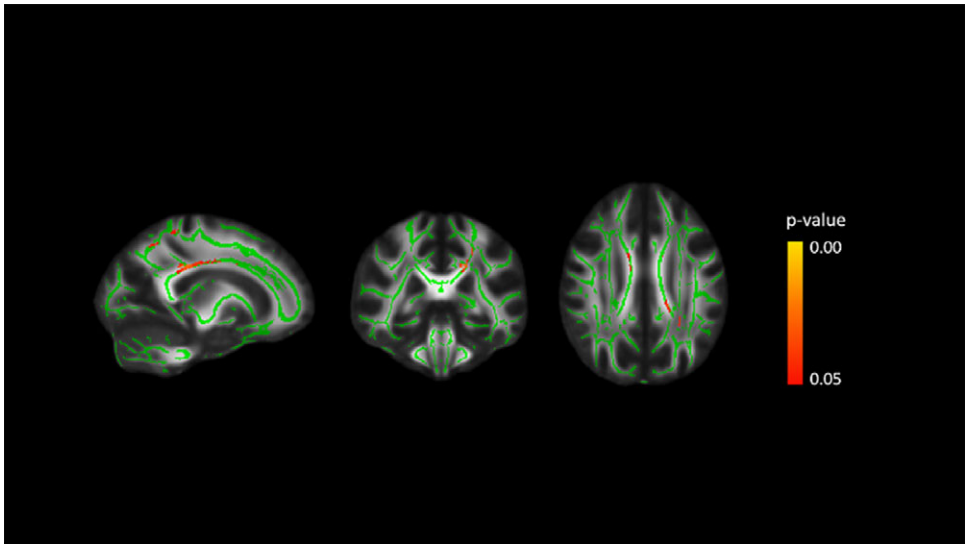

Figure 1. Cluster of reduced FA in the splenium of CC in TRS as compared with non-TRS ($x = -19$, $y = -34$, $z = -32$). Significant cluster ($P < .05$, corrected by TFCE) highlighted in red; yellow was shown on the mean FA image.

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initial diagnosis and treatment. Also, these findings may be a marker of resistance to treatment with antipsychotic medications currently available; however, this hypothesis has not been tested longidutinally.[38]

In agreement with our findings, Mitelman et al found a decrease in the FA of the splenium of the CC of patients with TRS relative to those of patients with non-TRS;[35] a follow-up study revealed that TRS patients showed a more pronounced decline in the size, but a less pronounced decline in the anisotropy, of the CC relative to their counterparts with non-TRS, suggesting that changes in the CC of the former occur earlier in the course of the disease—closer to the first psychotic episode—but stabilize in the chronic phases of the condition.[36] These findings support the role of a lower FA in the splenium of the CC as a biomarker of TRS.

A meta-analysis of voxel-based DTI studies has also reported reduced FA in the CCs of patients with schizophrenia relative to healthy controls.[39] Similarly, a meta-analysis found GM and WM abnormalities in the CCs of patients with schizophrenia.[40] The ENIGMA DTI study of microstructural white matter changes also found extensive CC changes and FA reductions in 20 of the 25 regions of interest, involving all major WM fasciculi,[9] supporting the hypothesis of structural dysconnectivity in schizophrenia.

Our analysis did not detect increases in clozapine-naïve RD, AD, or MD in the CCs of patients with TRS relative to those with non-TRS; hence, our study failed to show differences in microstructural organization between the two populations. However, no DTI measurement corresponds to one specific property; all diffusion parameters are considered to indicate the status of several tissue properties, such as myelinization, axonal orientation, and axonal density.[41,42] Indeed, research has found that changes in white matter microstructure pathologies may cause unpredictable changes in AD and RD that do not correspond to the tissue organization; hence, these diffusion indices may not always be reliable.[43]

This study benefits from having examined a larger, more homogeneous sample than have similar studies. Our results thus feature relatively robust validity. While our findings may have been confounded by the exposure of patients to psychotropic medications, the observed changes were not correlated to the dose of antipsychotic medication received. We used no objective adherence measures to ensure compliance in the trials before the TRS diagnosis. We used the 12-direction protocol in a 1.5 T field, although DTI protocols with more diffusion directions may be optimal. Seo et al[44] demonstrated that the FA values in large white matter bundles, such as the CC, were not affected by the number of gradient directions, acquisitions, and field strengths. The present study was further limited by not having included healthy controls for comparison in the study. As the current report is cross-sectional in nature, longitudinal studies are required to answer these questions and assess changes in TRS patients over time.

Conclusion

In conclusion, the present study detected a localized reduction in the FA of the CCs of a group of patients with TRS. The diminished FA of the CC may thus feature potential as a biomarker for TRS.

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