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ORIGINAL PAPER

Disrupted white matter integrity of corticopontine-cerebellar circuitry in schizophrenia

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Abstract Evidence for white matter abnormalities in patients with schizophrenia is increasing. Decreased fractional anisotropy (FA) in interhemispheric commissural fibers as well as long-ranging fronto-parietal association fibers belongs to the most frequent findings. The present study used tract-based spatial statistics to investigate white matter integrity in 35 patients with schizophrenia and 35 healthy volunteers. We found that patients exhibited significantly decreased FA relative to healthy subjects in the corpus callosum, the cerebral peduncle, the left inferior fronto-occipital fasciculus, the anterior thalamic radiation, the right posterior corona radiata, the middle cerebellar peduncle, and the right superior longitudinal fasciculus. Increased FA was detectable in the inferior sections of the corticopontine-cerebellar circuit. Present data indicate extended cortical-subcortical alterations of white matter integrity in schizophrenia using advanced data analysis strategies. They corroborate preceding findings of white matter structural deficits in mainly long-ranging association fibers and provide first evidence for neuroplastic changes in terms of an increased directionality in more inferior fiber tracts.

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Introduction

The disorder of schizophrenia is characterized by a diversity of symptoms. A disrupted connectivity in the cortical and subcortical pathways has been hypothesized as one pathophysiological mechanism underlying the heterogeneous psychopathology [1]. In accordance with this theory, evidence for disruptions in white matter pathways within prefrontal, parietal and temporal lobes in patients, as well as abnormalities within the fiber bundles connecting these regions is increasing [24, 28, 32, 67]. Thus, the superior longitudinal fasciculus, which constitutes the most relevant fronto-parietal fiber tract has been found to exhibit decreased structural integrity in patients with schizophrenia [6, 29, 52]. With regard to fronto-temporal connections the cingulum bundle [15, 47, 51] and the uncinate fasciculus [6, 40, 45, 47] have been reported to be significantly affected in patients. Here, the cingulum bundle might be of particular psychopathological relevance [22].

The majority of all findings, however, point to an impaired white matter integrity in predominantly posterior parts of the corpus callosum [8, 11, 14, 16, 48] suggesting an altered interhemispheric connectivity in schizophrenia patients as has previously been revealed by fMRI studies on functional connectivity [35, 49]. Some studies also found no white matter alterations in patients compared to healthy subjects [44, 56, 62] or increased fractional anisotropy (FA) [21, 37]. These increases in FA were located primarily in the temporo-parietal region of the arcuate fasciculus, the anterior corpus callosum, and regional frontal and cingulate white matter and have partly

been associated with the pathogenesis of auditory hallucinations [57]. Despite their heterogeneity, findings give reason to assume that decreased white matter integrity in various, predominantly prefrontal, parietal, and temporal pathways might play a central role in the pathophysiology of the disorder.

The present study applied a novel analysis technique to further investigate potential white matter alterations in a sample of subacute schizophrenia patients. As the voxel-wise analysis of FA images that most preceding studies used possesses several methodological drawbacks (like limited accuracy in between-subject anatomical coregistration or lacking standards for smoothing kernel size) the present study aimed at circumventing some of these limitations by performing tract-based spatial statistics (TBSS), a recently developed method for voxel-wise analysis of DTI data [53]. This method uses nonlinear registration and projects the center of fiber tracts of individual subjects into a common white matter skeleton thus avoiding residual misregistration issues of earlier methods. In addition, TBSS does not require image smoothing and uses permutation tests with a correction of multiple comparisons. Applying this method, we expected to minimize the probability of false-positive results and to be able to corroborate the most frequently reported finding of impaired white matter integrity in patients in the corpus callosum as the major interhemispheric pathway. This finding would substantiate results from our functional connectivity studies that indicated altered interhemispheric connectivity in subacute schizophrenia patients [49]. Second, we hypothesized to reveal white matter abnormalities predominantly in fiber tracts connecting cognitively relevant frontal and parietal areas (i.e., the superior longitudinal fasciculus) in concordance with the assumption that these abnormalities might constitute the structural basis of the repeatedly reported alterations in functional connectivity and associated cognitive deficits [13, 65].

Materials and methods

Subjects

The study included 35 right-handed patients (23 male, 12 female) with a DSM-IV diagnosis of schizophrenia who were in remission from acute psychosis and 35 right-handed healthy subjects (23 male, 12 female). Controls were matched to the patients according to age and years of education (means ± 2). On average, patients were 26.34 (SD = 7.13) years old and had a mean education of 11.43 (SD = 1.77) years. In the healthy controls, mean age was 26.20 (SD = 5.78) and mean education 12.66 (SD = 0.97) years. There was no significant difference between the groups in terms of age [$t(68) = 0.09$, $p = 0.93$] but a significant difference regarding education [$t(52.7) = -3.60$, $p < 0.01$, corrected degrees of freedom due to unequal variances]. Diagnosis was established using a symptom checklist on the basis of DSM-IV criteria (abbreviated SCID interview) and confirmed by two clinical psychiatrists (R.S. and Ch.S.). Patients were free of any concurrent psychiatric diagnosis and had no neurological conditions. All patients were in remission from an acute psychotic episode. Twenty patients were on stable medication with atypical antipsychotics (Olanzapine $n = 4$, Risperidone $n = 4$, Quetiapine $n = 4$, Clozapine $n = 2$, Aripiprazole $n = 1$, Risperidone plus Clozapine $n = 1$, Olanzapine plus Risperidone $n = 1$, Amisulpride plus Olanzapine $n = 1$, Amisulpride plus Quetiapine $n = 2$), 14 patients were unmedicated at measurement time point, and one patient was taking atypical antipsychotic medication (Haloperidole $n = 1$). The mean chlorpromazine equivalent (CPZ) dose [2, 64] was 413.9 mg (SD = 294.1). Patients had a mean duration of illness of 3.0 (SD = 3.7) years. Psychopathological status was assessed by the Positive and Negative Syndrome Scale [26]. Ratings were 19.5 (SD = 7.0) on the Positive Symptom Scale, 17.9 (SD = 6.6) on the Negative Symptom Scale, and 40.5 (SD = 13.6) on the General Psychopathology Scale.

Volunteer subjects were screened by comprehensive assessment procedures for medical, neurological, and psychiatric history. Exclusion criteria were current and potentially interfering medical conditions, any current or previous neurological or psychiatric disorder including brain trauma, substance abuse, and first-degree relatives with axis I psychiatric or neurological disorders. All participants gave written informed consent to a study protocol approved by the Ethics Committee of the Friedrich-Schiller-University Medical School. The study was undertaken in compliance with the principles of the Declaration of Helsinki.

DTI procedure

Data were collected on a 1.5 T Magnetom Vision whole body system (Siemens Medical Solutions, Erlangen, Germany) equipped with the standard CP transmit/receive head coil. Foam pads were used for positioning and immobilisation of the subject's head within the head coil.

Diffusion-weighted images were obtained using echo-planar imaging with a twice-refocused spin-echo sequence (TR = 4,000 ms, TE = 220 ms, field-of-view = 256 × 256 mm, slice thickness = 3 mm, NEX = 4, matrix = 96 × 128, no interslice gap) [46]. Diffusion-sensitizing gradient encoding was applied in six different directions with a diffusion-weighting factor of $b = 940$ s/mm^2. Additionally, images with no diffusion weighting (b_0-images) were

also acquired [17]. Images were acquired parallel to the anterior-posterior commissure in two blocks of 22 slices each, with one block covering the superior and the other one covering the inferior half of the brain. This provided a scan that covered almost the entire brain except the lower cerebellum and brainstem.

Data analysis

Movement and eddy current correction, masking, estimation of the diffusion tensor, and computation of anisotropy indices was performed with the SPM2 Diffusion II—toolbox provided by Volkmar Glauche (http://sourceforge.net/projects/spmtools). All subsequent image processing was performed using the FSL (FMRIB Software Library, FMRIB, Oxford, UK) software package [54]. Voxel-wise analysis was calculated using TBSS [53]. First, all subjects' FA images were nonlinearly normalized to a group-specific target image before the entire aligned data set was affine-transformed into $1 \times 1 \times 1\ \mathrm{mm}^3$ MNI 152 space (Montreal Neurological Institute, McGill, USA). Then, a mean FA image was created and filtered to retain only the center of the white matter tracts so as to create the mean FA skeleton. A threshold of FA > 0.4 was applied to the skeleton to include only major fiber bundles. Afterward, each subject's aligned FA image was projected onto the mean FA skeleton in order to account for residual misalignments between subjects after the initial nonlinear registration [53]. All voxel-wise group comparisons were performed using two-tailed two-sample t tests. The group-specific mean FA skeleton was used as a mask. The significance threshold for between-group differences was set at $p < 0.005$ (fully corrected for multiple comparisons across space) using the threshold-free cluster-enhancement option (TFCE) ($H = 2$, $E = 0.5$, neighbor-connectivity 26, extent 100, number of permutations = 500, for details regarding method and parameters see Smith and Nichols [55]). The TFCE method takes a raw statistic image and produces an output image in which the voxel-wise values represent the amount of cluster-like local spatial support. The white matter atlas by Mori et al. [38] was used for precise identification of the fiber tracts. The Matlab image processing toolbox (http://www.mathworks.com) and in-house software was employed for exact tract description (i.e. determination of tract extent and centroids). All images were inspected for anomalies and potential artefacts.

Results

Decreased FA in patients compared to controls ($p < 0.005$, nonparametric permutation test, corrected for multiple comparisons) was found in the corpus callosum, the cerebral peduncle, the left inferior fronto-occipital fasciculus, the superior sections of the corticopontine tract/anterior thalamic radiation, the right posterior corona radiata, and the anterior and lateral bundles of the middle cerebellar peduncle. With regard to fronto-parietal association fibers the right superior longitudinal fasciculus exhibited significantly decreased FA in patients compared to controls (Table 1, Figs. 1, 2). Increased FA in patients compared to controls ($p < 0.005$, nonparametric permutation test, corrected for multiple comparisons) was detectable in the inferior sections of the corticopontine tract and the posterior/medial sections of the middle cerebellar peduncle (Table 2, Fig. 2).

Figure 3 displays mean FA for patients and controls in all tracts which exhibited significant differences in FA between the groups.

Discussion

The present sample of subacute schizophrenia patients exhibited white matter anisotropy reductions in multiple cortical and subcortical fasciculi in association with distinct white matter anisotropy increases in the cortico-pontine-cerebellar tract. Most conspicuously and in concordance with our hypothesis significantly reduced white matter integrity in the splenium (including parts of the body) of the corpus callosum was detectable in patients relative to healthy volunteers. This finding corroborates the results of several preceding studies reporting a significantly decreased FA in the splenium of the corpus callosum in patients with schizophrenia [10, 11, 14]. It also corresponds to earlier fMRI findings that demonstrated a significantly decreased interhemispheric functional connectivity in sub-

Table 1 Significantly decreased FA in patients compared to controls at $p < 0.005$ corrected for multiple comparisons

FA patients < controls	x	y	z	k
Corpus callosum	93	100	103	454
Cerebral peduncle	102	116	55	348
Inferior fronto-occipital fasciculus	118	47	94	344
Corticopontine tract	78	120	64	197
Corticopontine tract/ant. thalamic radiation	71	140	79	119
Posterior corona radiata	67	74	104	133
Superior longitudinal fasciculus	44	100	115	102
Middle cerebellar peduncle	61	83	29	223
	122	81	25	127
	96	89	27	126
	85	89	25	124

x-, y-, z-coordinates in FSL notation, k number of voxels in tract

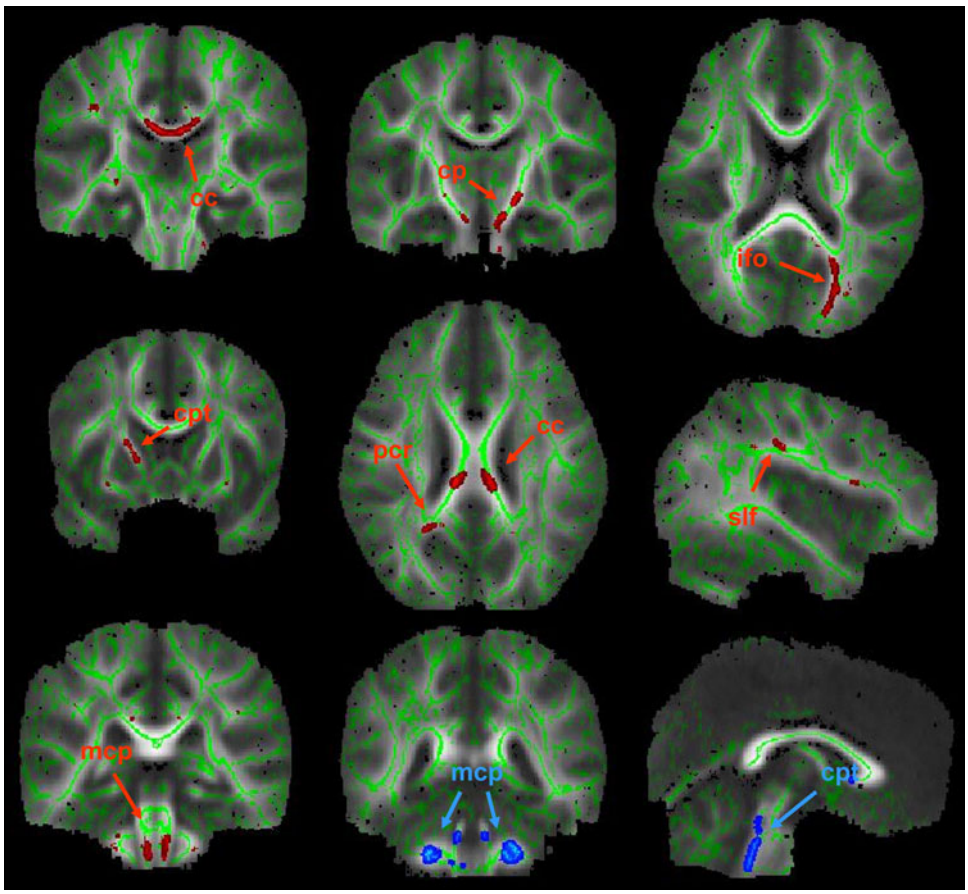

Fig. 1 Significant differences in FA between groups ($p < 0.005$, nonparametric permutation test, corrected for multiple comparisons). *Green* indicates white matter skeleton where no differences were found, *red* indicates significantly decreased FA in patients compared to controls, *blue* indicates significantly increased FA in patients compared to controls. Note that the right side of the subjects corresponds to the left side of the images. *cc* corpus callosum, *cp* cerebral peduncle, *ifo* inferior fronto-occipital fasciculus, *cpt* corticopontine tract, *pcr* posterior corona radiata, *slf* superior longitudinal fasciculus, *mcp* middle cerebellar peduncle

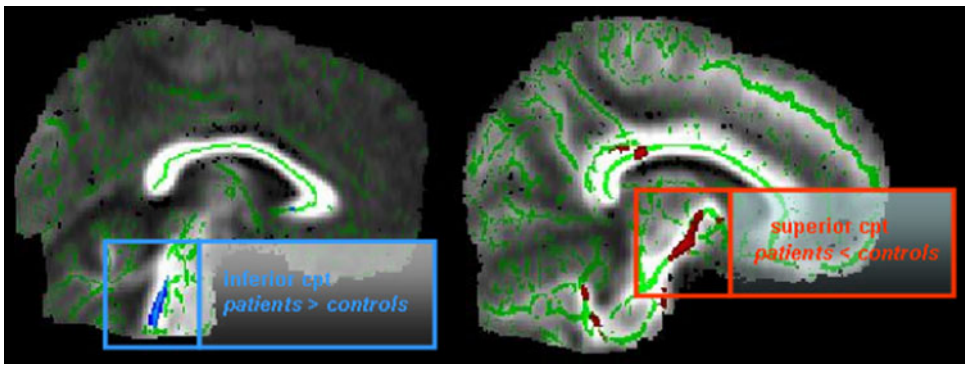

Fig. 2 Significant differences in FA between groups ($p < 0.005$, nonparametric permutation test, corrected for multiple comparisons) with decreased FA in patients compared to controls in superior pontine sections of the corticopontine tract (*red*) and significantly increased FA in patients compared to controls in more inferior parts (*blue*)

Table 2 Significantly increased FA in patients compared to controls at $p < 0.005$ corrected for multiple comparisons

FA patients > controls	*x*	*y*	*z*	*k*
Middle cerebellar peduncle	113	81	29	405
	63	80	28	365
Corticopontine tract	89	85	30	375

x-, *y*-, *z*-coordinates in FSL notation, *k* number of voxels in tract

chronic schizophrenia patients [35, 49] and substantiates the assumption that structural abnormalities, also with regard to size and shape, of the corpus callosum might be of major psychopathological relevance to the disorder [60]. As several other disorders that go along with structural alterations in the corpus callosum (like e.g., Andermann's and Apert's syndrome) are known to be associated with schizophrenia-like psychosis a close relation between callosal deficits and psychotic illness has been assumed [61]. Apart from the callosal alteration we found significantly decreased white matter integrity in patients relative to controls in the right and left cerebral peduncle, the left inferior fronto-occipital fasciculus, and the right posterior corona radiata. These findings are in line with studies by Hao et al. [19] and Cheung et al. [8] who reported a

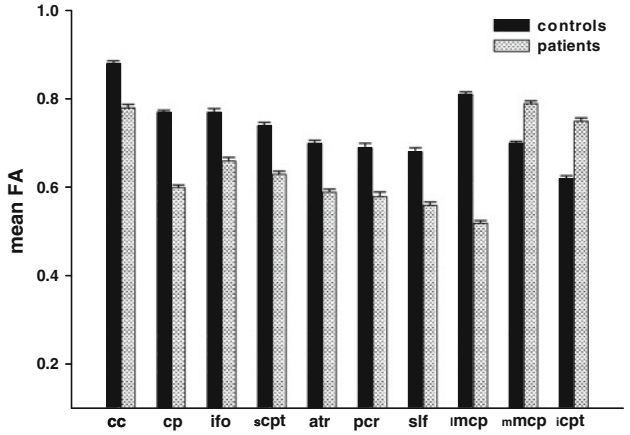

Fig. 3 Mean FA in patients and controls for tracts showing significant FA differences between the groups ($p < 0.005$, nonparametric permutation test, corrected for multiple comparisons). *cc* corpus callosum, *cp* cerebral peduncle, *ifo* inferior fronto-occipital fasciculus, *icpt* corticopontine tract (inferior), *scpt* corticopontine tract (superior), *atr* anterior thalamic radiation, *pcr* posterior corona radiata, *slf* superior longitudinal fasciculus, *mmcp* middle cerebellar peduncle (medial), *lmcp* middle cerebellar peduncle (lateral)

reduced FA in the right corona radiata, the left inferior fronto-occipital fasciculus and the left cerebral peduncle in patients with first-episode schizophrenia. They, moreover, correspond to recent findings by Walterfang et al. [59] who revealed a reduced white matter volume in the region of the fronto-occipital fasciculus in patients with psychosis.

In concordance with our hypothesis, patients exhibited significantly decreased FA in the superior longitudinal fasciculus. This finding adds to an increasing number of studies indicating white matter alterations in this fiber bundle in patients with schizophrenia [6, 29, 52]. Two other studies using TBSS to investigate white matter alterations in schizophrenia also revealed decreased FA in the superior longitudinal fasciculus [10, 25]. Douaud et al. [10] reported a significantly reduced white matter integrity in the arcuate component of the left superior longitudinal fasciculus in a sample of adolescent-onset schizophrenia patients. Karlsgodt et al. [25] found decreased FA in the superior longitudinal fasciculus bilaterally in young adult patients with recent-onset schizophrenia. The superior longitudinal fasciculus connects lateral prefrontal and parietal areas, which are known to play a relevant role in the context of various kinds of cognitive processes [58] and which have been shown to be abnormally activated during cognitive processing in schizophrenia [27, 50]. The decreased integrity of this pathway might constitute the structural basis of the disturbed fronto-parietal functional connectivity that has been reported in association with cognitive deficits in schizophrenia patients before [20, 65]. Accordingly, it has been postulated that sustained neuronal activation during cognitive processing may be mediated by reverberating activity of a large-scale neural network [63] within which the long-range cortico-cortical projections like the superior longitudinal fasciculus or fronto-occipital fasciculus constitute central components. Consequently, deficits of these projections would lead to deficient functional connectivity within this network and associated cognitive impairments [20]. Recent results by Forstmann et al. [12] who detected a relation between individual cognitive control capacities and fronto-occipital fasciculus integrity corroborate this assumption.

In correspondence with several preceding studies [10, 42, 62], we detected altered white matter integrity also in corticopontine and middle cerebellar tracts. The corticopontine projections, which originate in mainly (pre)motor (BA 4/6), somatosensory (BA 1/2/3), and parietal (BA 5) areas connect the cortex with the pons which, in turn, is connected to the cerebellum via the middle cerebellar peduncle [18]. This cerebro-ponto-cerebellar loop is known to be predominantly involved in the execution of learned movements, the sensory guidance of movements as well as in the execution of visually guided saccades (smooth-pursuit eye movements) in primates [4]. Disturbance of this loop leads to disturbed smooth-pursuit eye movements and motor deficits or neurological soft signs that constitute well-known characteristics of the disorder of schizophrenia [9, 33]. Thus, the decreased white matter integrity that the present patient sample exhibited in more superior sections of the corticopontine tract next to the pons might constitute the structural correlate of these frequently reported symptoms. Interestingly, more inferior sections of the corticopontine tract as well as the medial parts of the middle cerebellar peduncle exhibited an increased FA in patients compared to controls. Results on cortical plasticity indicate that disruption to inhibitory systems leads to overactivity and axonal sprouting/remyelination within downstream networks [36, 61]. As the corticopontine tract sends inhibitory GABAergic projections to the pons [5], the decreased integrity of these projections might be the cause for the increased myelination further downstream. Animal studies on functional recovery after lesions in rats indicating that plasticity in the corticopontine tract is strong [66] support this presumption. Further studies are needed, however, to prove this somewhat speculative assertion. Recent findings indicating increased white matter volumes in the caudate nucleus after treatment with olanzapine in patients with schizophrenia [43], moreover, suggest that the antipsychotic medication which most patients of the studied sample were treated with might also play a role. Atypical antipsychotics have been shown to increase brain-derived neurotrophic factor (BDNF) mRNA expression in rats [3]. Since BDNF is known to enhance synaptic plasticity and axonal myelination this might be another underlying mechanism. Independent of the mechanisms

involved, present results of white matter alterations in corticopontine and middle cerebellar tracts confirm earlier findings [10, 41, 62], predominantly results by Okugawa et al. [41] who found a negative correlation between FA in superior cerebellar peduncle and cognitive function. They postulated a neural disorganization in the cerebellar peduncle in patients, which leads to worse cognitive function despite increased FA. Our data showing both relative increases and decreases in the cerebellar peduncle support the notion of a neural disorganization within these pathways in schizophrenia.

Finally, when discussing the mechanisms underlying structural alterations in schizophrenia neurodevelopmental aspects should not remain unaddressed. Studies investigating the association between illness duration and white matter alterations post hoc, which found no correlation [11, 23, 30, 31] suggest stable alterations that may be even present prior to the clinical onset of the disease. However, validity of post hoc correlations is generally limited. Methodologically, more reliable studies that took the neurodevelopmental aspect into account by analyzing patient groups at different stages of the illness [14, 34] indicate that alterations in white matter structure might progress across the course of the disorder. In their recent study, Meisenzahl et al. [34] compared white matter alterations in patients with recurrent schizophrenia with alterations in a sample of first-episode patients and found less white matter reduction in the hippocampus in the first episode group. In a longitudinal study by Cahn et al. [7], however, no correlation between duration of psychosis and white matter volume change was detectable. Methodological variabilities (regarding sample size, analysis methods, age, or medication) might account for the heterogeneity in findings. Further longitudinal studies controlling for confounding methodological effects would certainly further understanding of the neurodevelopmental origins of white matter alterations in schizophrenia.

Limitation of the study

The application of only six diffusion directions has to be mentioned as a methodological limitation of the present study. There is growing consensus that DTI with 20 or even 30 diffusion directions increases signal-to-noise and allows for a more precise characterization of fiber directionality [39].

Conclusion

Taken together, the present study provides further evidence for extended cortical-subcortical alterations of white matter integrity in schizophrenia. Most interestingly, aside from lowered FA values, in particular in callosal and fronto-parietal fiber tracts, increased FA values could be observed in subcortical-cerebellar circuitry. Therefore, the present data using advanced data analysis strategies by employing tract-based statistics shed further light on the potentially heterogeneous neuronal white matter changes in schizophrenia. Aside from the notion of mere structural deficits, the present data suggest neuroplastic changes within white matter fiber tracts of schizophrenia. A more detailed study of functional connectivity changes in combination with the specific tract-based alterations appears a promising strategy for further studies.

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