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ARTICLE OPEN

Reduced fronto–striatal white matter integrity in schizophrenia patients and unaffected siblings: a DTI study

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BACKGROUND: Schizophrenia is characterized by impairments in the fronto–striatal network. Underlying these impairments may be disruptions in anatomical pathways connecting frontal and striatal regions. However, the specifics of these disruptions remain unclear and whether these impairments are related to the genetic vulnerability of schizophrenia is not known.
METHODS: Here, we investigated fronto–striatal tract connections in 24 schizophrenia patients, 30 unaffected siblings, and 58 healthy controls using diffusion tensor imaging. Mean fractional anisotropy (FA) was calculated for tracts connecting the striatum with frontal cortex regions including the dorsolateral prefrontal cortex (DLPFC), medial orbital frontal cortex, and inferior frontal gyrus. Specifically, the striatum was divided into three subregions (caudate nucleus, putamen, and nucleus accumbens) and mean FA was computed for tracts originating from these striatal subregions.
RESULTS: We found no differences between patients, siblings, and controls in mean FA when taking the whole striatum as a seed region. However, subregion analyses showed reduced FA in the tract connecting the left nucleus accumbens and left DLPFC in both patients ($P = 0.0003$) and siblings ($P = 0.0008$) compared with controls.
CONCLUSIONS: The result of reduced FA in the tract connecting the left nucleus accumbens and left DLPFC indicates a possible reduction of white matter integrity, commonly associated with schizophrenia. As both patients and unaffected siblings show reduced FA, this may represent a vulnerability factor for schizophrenia.

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INTRODUCTION

Underlying the clinical and cognitive symptoms in schizophrenia may be dysfunctions of the frontal lobe and the striatum.[1–5] Indeed, functional magnetic resonance imaging (MRI) studies have demonstrated abnormal fronto–striatal activity.[1–3,6–9] Moreover, structural MRI studies have revealed reductions in brain volume of the frontal cortex[10–12] and striatum[11,13] in schizophrenia patients.

In addition to functional and structural brain measurements, anatomical pathways connecting frontal and striatal regions may also be disrupted in schizophrenia. Two studies have investigated fronto–striatal white matter tracts using diffusion tensor imaging (DTI). Quan *et al.*[14] reported reduced fractional anisotropy (FA) in the tract connecting the left inferior frontal gyrus (IFG) with the striatum in 16 schizophrenia patients compared with 18 matched controls.[14] However, they only compared tracts connecting frontal regions with the whole striatum, using the striatum as a single seed region, rather than subdividing it into specific subregions. This subdivision is important as different striatal components are involved in specific functional networks.[15] Indeed, Bracht *et al.*[16] investigated white matter tracts connecting the nucleus accumbens with frontal and subcortical regions in schizophrenia patients ($n = 24$) and controls ($n = 22$).[16] They reported on increased probability indices forming part of a bundle of interest for the tract connecting the nucleus accumbens with the dorsolateral prefrontal cortex (DLPFC), suggesting reduced white matter tract integrity. However, they did not find a difference in FA in this tract. This inconsistency makes it unclear whether and how this white matter tract is impaired by schizophrenia. Furthermore, in both the studies, it remains unclear whether these fronto–striatal white matter tract dysfunctions are related to the illness itself or to a genetic vulnerability for the disorder.

Therefore, we investigated fronto–striatal tracts in a large cohort of schizophrenia patients, unaffected siblings, and matched healthy controls using DTI. Siblings do not have the illness, but share on average 50% of their genes with their ill relative.[17] Furthermore, they have a 10-fold increased risk to develop schizophrenia.[18] Consequently, if siblings show impairments in fronto–striatal tract connections similar to those observed in patients this would provide evidence in support for a genetic vulnerability underlying this phenotypic abnormality. Fronto–striatal tract abnormalities in siblings are anticipated given reports on functional[1,6,19–22] as well as structural abnormalities[10,11,23] in this network. Moreover, abnormalities in white matter integrity have already been shown in siblings in other brain regions including the fasciculus arcuatus,[24–26] medial frontal cortex,[27] prefrontal cortex,[28] cingulate and angular gyri,[29] inferior occipitofrontal fasciculus,[25] anterior limb of the internal capsules,[26] corpus callosum genu,[30] cuneus,[31] and temporal lobe.[30]

Here, we examined FA in fronto–striatal pathways using DTI in 24 schizophrenia patients, 30 unaffected siblings, and 58 healthy controls. FreeSurfer software[32] was used to parcellate the gray matter regions used to trace the fiber bundles of interest. We subdivided the frontal cortex into three regions: DLPFC, medial orbital frontal cortex (mOFC), and IFG, all of which are consistently reported to be abnormal in schizophrenia patients and their siblings in functional[1,8,21] as well as structural MRI studies.[10,33] Neurons from these frontal regions project to the caudate nucleus, putamen, and nucleus accumbens separately, together forming the fronto–striatal network.[34] Mean FA was then computed along

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averaged tracts starting in each of these striatal subregions directing to the frontal cortex regions.

Given reports on reduced FA in various tracts (for recent review, see Fitzsimmons *et al.*[35]), we hypothesize that FA in fronto–striatal white matter tracts will be reduced in schizophrenia patients. Furthermore, we hypothesize that if these deficits signify a genetic vulnerability, then similar deficits are also present in unaffected siblings of schizophrenia patients.

MATERIALS AND METHODS

Participants

Twenty-four schizophrenia patients, 30 unaffected siblings, and 58 healthy control subjects participated in this study. All subjects were right-handed and there were no differences between groups for age and gender (Table 1). None of the participants had any contraindications for MRI or suffered from alcohol or drug dependence, which was assessed with the Composite International Diagnostic Interview. The patients were outpatients recruited from the Department of Psychiatry at the University Medical Center Utrecht and participating in an ongoing longitudinal study.[36] The diagnosis of schizophrenia, schizophreniform, or schizoaffective disorder in patients was assessed with the Structured Clinical Interview for DSM-IV or the Comprehensive Assessment of Symptoms and History.[37] Symptom severity in terms of positive, negative, and general symptoms were assessed with the positive and negative syndrome scale (PANSS).[38] All schizophrenia patients received antipsychotic medication (medication use is listed in Supplementary Information). Four siblings had a history of at least one depressive episode, as verified by the Comprehensive Assessment of Symptoms and History. None of the healthy control subjects had a history of a neurological or psychiatric diagnosis as verified by either the Mini-International Neuropsychiatric Interview[39] or the Schedules for Clinical Assessment in Neuropsychiatry (SCAN 2.1).[40] Healthy control subjects who had a first-degree relative suffering from a psychotic disorder were excluded. The participants received monetary compensation for participation. All gave written informed consent. The ethics committee of the University Medical Center of Utrecht approved this study.

Diffusion tensor imaging

Image acquisition and preprocessing. A T1-weighted structural MRI scan and a set of two diffusion-weighted imaging (DWI) scans were obtained from each subject using a 3.0 T Achieva scanner (Philips, Best, The Netherlands). One three-dimensional T1-weighted scan (185 slices; repetition time = 8.4 ms; echo time = 3.8 ms; flip angle = 8°; field of view, 252 × 185 × 288 mm; voxel size: 1 mm isotropic) of the whole head was made for anatomical reference. The T1-weighted scans were used to extract anatomically delineated regions of interest (ROIs) of the caudate nucleus, putamen, nucleus accumbens, DLPFC (consisting of the rostral middle frontal gyrus[41]), mOFC, and IFG, consisting of the pars opercularis, pars orbitalis, and pars triangularis; Figure 1, Figure 2) in each hemisphere using the FreeSurfer 5.1.0 structural imaging pipeline.[32]

A set of two transverse DWI scans were acquired (30 diffusion-weighted volumes with different non-collinear diffusion directions with b-factor = 1,000 s/mm^2 and eight diffusion-unweighted volumes with b-factor = 0 s/mm^2; parallel imaging SENSE factor = 2.5; flip angle = 90°; 60 slices of 2.5 mm; no slice gap; 96 × 96 acquisition matrix; reconstruction matrix 128 × 128; FOV = 240 mm; TE = 88 ms; TR = 9,822 ms; no cardiac gating; and total scan duration = 296 s). The second DWI scan is identical to the first except that the k-space readout is reversed, which allows for correction of susceptibility artifacts during preprocessing. Preprocessing of the DWI scans was performed with the diffusion toolbox of Andersson *et al.*[42,43] and in-house developed software.[44] First, susceptibility artifacts were corrected by calculating a distortion map on the basis of the two b = 0 images

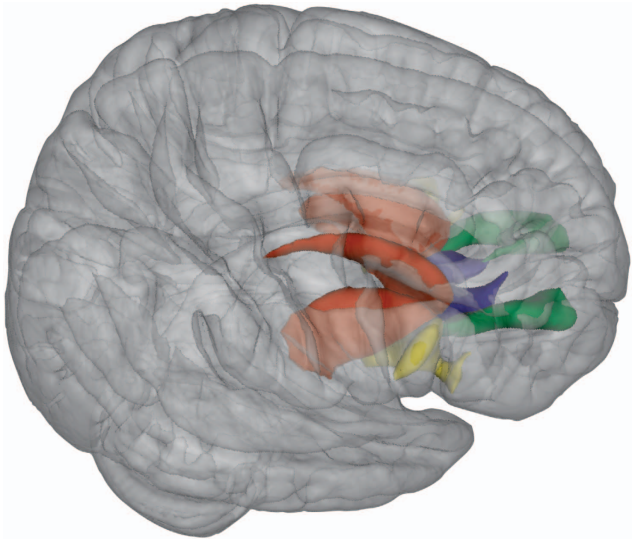

Figure 1. Mean fractional anisotropy was compared along averaged fibers connecting the striatum (red) with the frontal cortex regions: striatum–DLPFC (green), striatum–mOFC (blue), and striatum–IFG (yellow). Right = right.

Table 1. Demographic characteristics of the diagnostic groups

	HC (n = *58*)	*SB* (n = *30*)	*SZ* (n = *24*)	*Test statistic*	P
Age (years)	28.8 ± 1.0	31.4 ± 1.2	31.1 ± 0.7	F = 2.04	0.14
Gender (M/F)	35/23	17/13	19/5	χ^2 = 3.39	0.18
Participant's education level	7.2 ± 0.2	6.3 ± 0.3	4.8 ± 0.4	F = 15.10	< 0.001
Father's education level	5.2 ± 0.5	5.6 ± 0.5	5.4 ± 0.5	F = 0.23	0.80
Mother's education level	4.9 ± 0.5	5.4 ± 0.4	4.6 ± 0.5	F = 0.85	0.43
Cigarette smokers	2	13	12	F = 1.68	0.20
Cigarettes per day	3.5 ± 1.5	10.4 ± 2.1	14.3 ± 3.7	F = 1.16	0.33
Duration of illness (years)			6.2 ± 0.9		
Paranoid/disorganized/undifferentiated type			23/0/0		
Schizoaffective disorder			1		
Chlorpromazine equivalent doses (mg)			321.5 ± 53.4		
PANSS positive symptoms score			14.5 ± 0.8		
PANSS negative symptoms score			13.3 ± 0.7		
PANSS general symptoms score			27.0 ± 1.1		
History of depressive episode		4			

Abbreviations: F, female; HC, healthy controls; M, male; PANNS, positive and negative syndrome scale; SB, unaffected siblings of schizophrenia patients; SZ, schizophrenia patients.
Values represent mean ± s.e.m. Level of education was measured on a 9-point scale ranging from no education (0) to university degree (8).

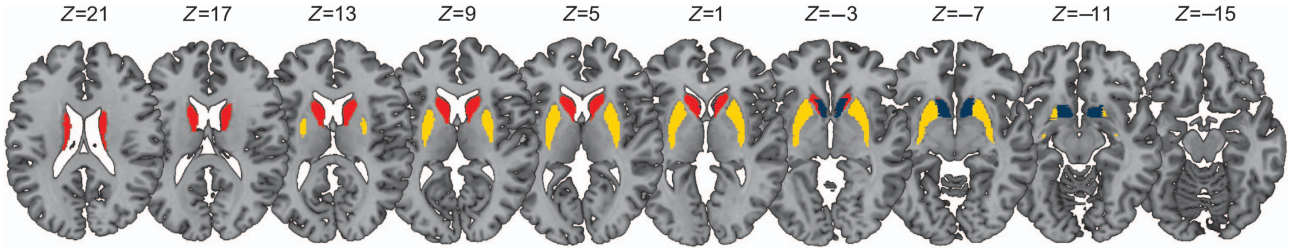

Figure 2. The striatum was divided into three subregions: nucleus accumbens (blue), caudate nucleus (yellow), and putamen (red), and mean fractional anisotropy was computed for tracts originating from these striatal subregions directing to frontal cortex regions including DLPFC, mOFC, and IFG. Right = right.

acquired with reversed k-space readout. Subsequently, it was applied to all DWI volumes. This resulted in one corrected DWI set consisting of a single b = 0 volume (averaged over eight b = 0 volumes) and 30 corrected weighted volumes.[43] Finally the DWI set was corrected for eddy-current distortions and small head movements.[42]

Fronto–striatal fiber tractography and diffusion parameter reconstruction. Diffusion modeling and probabilistic tractography were carried out using the FMRIB Diffusion Toolbox (FDT, version 2.0, http://fsl.fmrib.ox.ac.uk/fsl/fsl-4.1.9/fdt/fdt_probtrackx.html). This process involves generating connectivity distributions from user-specified seed voxels to target voxels. First, the whole striatum (nucleus accumbens, putamen and caudate nucleus) was used as a seed mask and the three ROI's of the frontal cortex (DLPFC, mOFC and IFG) were defined as target ROI's, such that for each subject three fiber distributions from striatum to frontal cortex were obtained (Figure 1). Each frontal ROI was specified as a waypoint and as a termination mask to ensure that only those streamlines running between the seed mask and target ROI were captured in the fiber distribution. The default parameters (5000 streamline samples, step length of 0.5 mm, and curvature threshold of 0.2) were used during the probabilistic fiber tracking procedure.

Subsequently, tracts originating from the three anatomical subregions of the striatum were analyzed separately by using these predefined ROIs as separate seed masks directing to the frontal cortex regions as described above (Figure 2). In this way, a total of 12 tracts were traced for and within each hemisphere between the frontal cortex and the striatum, leaving 24 fiber distributions for each subject in total.

Because the seed points could be volumetrically dependent on individual or group differences, a group average fiber was reconstructed for each of the 24 fiber distributions. First, the Tract Based Spatial Statistics toolbox (version 1.2)[45] was applied to subjects' FA maps for warping into FMRIB58_FA standard space. This nonlinear registration was also applied to each of the 24 individually obtained fiber distributions. By only selecting the top 1% of streamlines in each fiber distrubution that overlapped in all participating subjects, a total of 24 group average tracts were reconstructed. The group average tracts were made binary and subsequently they were projected onto the warped FA maps, allowing for the estimation of a mean FA measure per individual per tract.

Statistical analysis. Demographic data between schizophrenia patients, siblings, and healthy controls were compared using independent sample *t*-tests. General linear model (GLM) analyses were performed to test for effects of group (schizophrenia patients, siblings, and controls) on FA of the tracts connecting the striatum with the frontal regions (DLPFC, mOFC, and IFG). Subsequently, similar GLMs were performed to test for effects of group (schizophrenia patients, siblings, and controls) on FA of the tracts connecting the three subregions of the striatum (caudatus, putamen, and nucleus accumbens) with the frontal regions (DLPFC, mOFC, and IFG). All the results were Bonferroni corrected for multiple testing (three seeds × three targets × two hemispheres = 18), resulting a critical *P* value of 0.0028. In schizophrenia patients, Pearson's correlations were used to calculate associations between mean FA and symptom severity, as measured with the PANSS. Finally, as it has been shown that nicotine use may impact FA measures in fronto–striatal tracts,[46] we compared mean FA, using two-sample *t*-tests, between cigarette smokers and nonsmokers in the whole sample as well as in healthy controls, schizophrenia patients, and siblings.

Table 2. Fractional anisotropy for tracts connecting the whole striatum with the frontal cortex regions

	HC (n = *58*)	*SB* (n = *30*)	*SZ* (n = *24*)	P *(HC versus SB)*	P *(HC versus SZ)*	P *(SB versus SZ)*
Striatum–DLPFC						
R	0.36 ± 0.02	0.36 ± 0.02	0.36 ± 0.02	0.80	0.53	0.74
L	0.35 ± 0.02	0.34 ± 0.02	0.35 ± 0.02	0.67	0.25	0.17
Striatum–mOFC						
R	0.28 ± 0.01	0.28 ± 0.01	0.28 ± 0.01	0.71	0.97	0.73
L	0.26 ± 0.01	0.26 ± 0.01	0.26 ± 0.01	0.61	0.87	0.53
Striatum–IFG						
R	0.30 ± 0.01	0.30 ± 0.01	0.29 ± 0.01	0.96	0.30	0.33
L	0.28 ± 0.01	0.28 ± 0.01	0.28 ± 0.01	0.47	0.93	0.49

Abbreviations: DLPFC, dorsolateral prefrontal cortex; HC, healthy controls; IFG, inferior frontal gyrus; L, left; mOFC, medial orbital frontal cortex; R, right; SB, unaffected siblings of schizophrenia patients; SZ, schizophrenia patients.
Values represent mean ± s.d.

RESULTS

Group differences in fractional anisotropy

There were no significant differences among patients, siblings, and controls in mean FA along tracts averaged for the whole striatum with the frontal cortex regions (Table 2). However, when investigating tracts projecting from subregions of the striatum, schizophrenia patients as well as their unaffected siblings showed reduced mean FA in the tract between the left nucleus accumbens and left DLPFC (patients versus controls: $t(80) = 3.80$, $P = 0.0003$; siblings versus controls: $t(86) = 3.49$, $P = 0.0008$; Table 3). Patients and siblings did not differ ($t(52) = 0.56$, $P = 0.58$) indicating a similar reduction in FA. Symptoms severity in schizophrenia patients as measured with the PANNS scores did not correlate with mean FA in this tract (PANSS positive symptoms score: $r = 0.1$, $P = 0.65$, PANSS negative symptoms score: $r = -0.6$, $P = 0.77$, PANSS general symptoms score: $r = -0.2$, $P = 0.38$). Finally, smoking status did not affect mean FA for this tract in the whole sample ($t(60) = 0.68$, $P = 0.50$), nor in healthy controls ($t(8) = -1.86$, $P = 0.10$), schizophrenia patients ($t(20) = 0.45$, $P = 0.66$), or siblings ($t(28) = 0.68$, $P = 0.50$). Mean FA in the other tracts did not differ between the groups.

DISCUSSION

This study investigated fronto–striatal pathways in 24 schizophrenia patients, 30 unaffected siblings, and 58 healthy controls

Table 3. Fractional anisotropy for tracts connecting subregions of the striatum with the frontal cortex regions

	HC (n = *58*)	*SB* (n = *30*)	*SZ* (n = *24*)	P *(HC versus SB)*	P *(HC versus SZ)*	P *(SB versus SZ)*
Nucleus accumbens–DLPFC						
R	0.38 ± 0.02	0.37 ± 0.02	0.37 ± 0.02	0.16	0.22	0.92
L	0.35 ± 0.01	0.34 ± 0.02	0.33 ± 0.02	0.0008*	0.0003*	0.58
Nucleus accumbens–mOFC						
R	0.22 ± 0.01	0.21 ± 0.01	0.22 ± 0.01	0.24	0.63	0.55
L	0.21 ± 0.01	0.21 ± 0.02	0.21 ± 0.01	0.82	0.80	0.72
Nucleus accumbens–IFG						
R	0.27 ± 0.01	0.27 ± 0.02	0.27 ± 0.01	0.42	0.48	0.94
L	0.25 ± 0.01	0.25 ± 0.01	0.26 ± 0.01	0.92	0.10	0.16
Caudate–DLPFC						
R	0.37 ± 0.02	0.37 ± 0.02	0.37 ± 0.02	0.86	0.23	0.38
L	0.36 ± 0.02	0.35 ± 0.02	0.36 ± 0.03	0.57	0.17	0.09
Caudate–mOFC						
R	0.29 ± 0.02	0.29 ± 0.01	0.29 ± 0.02	0.70	0.92	0.80
L	0.28 ± 0.02	0.28 ± 0.01	0.29 ± 0.02	0.92	0.48	0.55
Caudate–IFG						
R	0.35 ± 0.01	0.35 ± 0.02	0.35 ± 0.01	0.78	0.19	0.20
L	0.33 ± 0.01	0.33 ± 0.02	0.33 ± 0.01	0.72	0.95	0.72
Putamen–DLPFC						
R	0.39 ± 0.02	0.39 ± 0.02	0.39 ± 0.02	0.89	0.75	0.86
L	0.38 ± 0.02	0.38 ± 0.02	0.39 ± 0.02	0.55	0.27	0.11
Putamen–mOFC						
R	0.32 ± 0.02	0.32 ± 0.02	0.31 ± 0.01	0.67	0.74	0.50
L	0.28 ± 0.02	0.28 ± 0.01	0.28 ± 0.01	0.41	0.91	0.51
Putamen–IFG						
R	0.26 ± 0.01	0.25 ± 0.01	0.25 ± 0.01	0.72	0.33	0.50
L	0.24 ± 0.01	0.24 ± 0.01	0.24 ± 0.01	0.45	0.84	0.37

Abbreviations: DLPFC, dorsolateral prefrontal cortex; HC, healthy controls; IFG, inferior frontal gyrus; L, left; mOFC, medial orbital frontal cortex; R, right; SB, unaffected siblings of schizophrenia patients; SZ, schizophrenia patients.
P values with * survived Bonferroni correction for multiple testing. Values represent mean ± s.d.

using DTI. Results show reduced functional anisotropy (FA) in the tract connecting the left nucleus accumbens and left DLPFC in schizophrenia patients as well as their unaffected siblings, indicating reduced white matter integrity compared with controls. Taken together with the fact that siblings share on average 50% of their genes with their ill relative, these results indicate that reduced white matter integrity in this tract may represent a vulnerability factor for schizophrenia.

Our finding of reduced FA in the tract connecting the left nucleus accumbens and left DLPFC is consistent with findings from Bracht *et al.*[16] who compared fronto–striatal tracts between 24 schizophrenia patients and 22 healthy controls. Although they did not find difference in FA, they computed a measure representing spatial extension of fiber tracts (probability indices forming part of a bundle of interest). They found this measure to be increased in schizophrenia patients compared with controls in the tract between the left nucleus accumbens and left DLPFC, and suggest this to indicate volume reduction of this white matter pathway. We replicated and extended this finding by showing decreased FA in this particular tract in schizophrenia patients. Moreover, we found a similar FA reduction in this tract in siblings of schizophrenia patients, indicating that this deficit may represent a vulnerability factor for schizophrenia.

We did not find reduced FA in schizophrenia patients or siblings when averaging over all tracts connecting the entire striatum and DLPFC. This is in line with data from Quan *et al.*,[14] who also did not find differences between schizophrenia patients ($n = 16$) and controls ($n = 18$) in FA values between tracts connecting DLPFC and striatum.[14] However, they did not investigate tracts originating from different subsections of the striatum.

Our finding of decreased mean FA in both schizophrenia patients and siblings may indicate decreased white matter integrity, as FA is used as an index for the microstructural integrity of white matter fiber bundles.[47] White matter integrity abnormalities as measured with DTI have been reported in schizophrenia patients and their unaffected siblings in several regions of the brain including the frontal lobe, hippocampus, and internal capsule.[24–30,35] In the present study, we extend these results by showing white matter integrity reductions in schizophrenia patients and siblings specifically in fibers connecting the left nucleus accumbens and left DLPFC. As we did not find deficits in other tracks, it is unlikely that our results are driven by a global impairment in white matter integrity. However, it should be noticed that the schizophrenia patients in our sample are relatively young, so it cannot be ruled out that progression of the illness over time may result in abnormalities of other white matter tracks.[48]

Both the nucleus accumbens and the DLPFC are part of reward pathways[49] and are known to be involved in delayed reward processing.[50,51] Our finding of reduced FA in this particular tract is

consistent with earlier reports on impaired fronto–striatal reward processing in schizophrenia patients[8,9] and siblings.[22,52] Our current finding of structural impairments in the reward pathway combined with previous reports of functional fronto–striatal impairments during reward processing adds to the evidence in support of fronto–striatal deficits representing a genetic vulnerability factor for schizophrenia.

The decrease in white matter integrity in schizophrenia patients was not related with symptom severity as measured with the PANSS. This was anticipated given that Bracht *et al.* also did not find such a relationship.[16] Furthermore, siblings showed similar white matter integrity reduction while being symptom-free. Taken together, this null finding is consistent with the notion that our finding of reduced white matter integrity in the tract connecting left nucleus accumbens and left DLPFC is related to the genetic vulnerability for schizophrenia rather than to the clinical manifestations.

Our study has several limitations which need to be addressed. Schizophrenia patients used antipsychotic medication which may have influence on white matter integrity.[53] However, this is not expected given that we have previously failed to show an effect of medication on white matter volume in schizophrenia patients.[54] Moreover, the fact that patients as well as unmedicated siblings show this deficit may indicate that this represents a genetic vulnerability for schizophrenia rather than a medication effect. However, common environmental factors cannot be ruled out. To quantify the influence of genetic factors on the observed reduction in white matter tract integrity, a discordant twin-design would be most suitable. As it has already been shown that white matter integrity is substantially heritable,[55] it is likely that genetic factors have a role in the effect observed in the present study. One other potential limitation is that the patients were not acutely ill as they show moderate PANSS score. However, as unaffected siblings also show decreased FA in the tract connecting the left nucleus accumbens and left DLPFC, it is unlikely that symptom severity impacts the structural impairment we report on. In contrast, it may very well be that patients that are more severely affected by the illness display FA impairments in additional white matter tracts.

Here, we show impairments in fronto–striatal pathways in schizophrenia patients as well as in unaffected siblings. Specifically, we found mean FA to be decreased in the tract connecting the left nucleus accumbens and left DLPFC. This result is in line with the notion that schizophrenia is characterized by fronto–striatal deficits. Moreover, the present data add to the evidence suggesting that fronto–striatal deficits represent genetic vulnerability factors for schizophrenia. Future research should focus on how this network develops in adolescents at genetic risk for schizophrenia.

CONTRIBUTIONS

MdL designed the study, contributed to writing of the study protocol, performed the literature searches, data acquisition and data analyses, and wrote the first draft of the manuscript. MMB contributed to the data analyses and writing of the manuscript. RCWM contributed to the data analyses. MV supervised the data acquisition and analyses, and contributed to the writing of the manuscript and the study protocol. RSK, end revision and guarantor, supervised the analyses and writing of the manuscript. All the authors contributed to and have approved the final manuscript.

COMPETING INTERESTS

MdL, MMB, RCWM, RSK, and MV declare no conflict of interest.

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