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Analyzing language ability in first-episode psychosis and their unaffected siblings: A diffusion tensor imaging tract-based spatial statistics analysis study

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ABSTRACT

Schizophrenia (SZ) is a highly heritable mental disorder, and language dysfunctions play a crucial role in diagnosing it. Although language-related symptoms such as disorganized speech were predicted by the polygenic risk for SZ which emphasized the common genetic liability for the disease, few studies investigated possible white matter integrity abnormalities in the language-related tracts in those at familial high-risk for SZ. Also, their results are not consistent. In this current study, we examined possible aberrations in language-related white matter tracts in patients with first-episode psychosis (FEP, $N = 20$), their siblings (SIB, $N = 20$), and healthy controls (CON, $N = 20$) by applying whole-brain Tract-Based Spatial Statistics and region-of-interest analyses. We also assessed language ability by Thought and Language Index (TLI) using Thematic Apperception Test (TAT) pictures and verbal fluency to see whether the scores of these language tests would predict the differences in these tracts. We found significant alterations in language-related tracts such as inferior longitudinal fasciculus (ILF) and uncinate fasciculus (UF) among three groups and between SIB and CON. We also proved partly their relationship with the language test as indicated by the significant correlation detected between TLI Impoverished thought/language sub-scale and ILF. We could not find any difference between FEP and CON. These results showed that the abnormalities, especially in the ILF and UF, could be important pathophysiological vulnerability indexes of schizophrenia. Further studies are required to understand better the role of language as a possible endophenotype in schizophrenia with larger samples.

1. Introduction

Schizophrenia is a highly heritable mental disorder (Gottesman, 1991; Lichtenstein et al., 2009; Hilker et al., 2018) and language dysfunctions play a crucial role in diagnosing it (Zimmerer et al., 2017; Pawełczyk et al., 2021). It is well known that these dysfunctions have been linked to white matter (WM) abnormalities in language-related brain regions. By analyzing the WM integrity in the fiber bundles, we can study the structural underpinnings of information transmission between distant areas of the language network (Cavellti et al., 2018). The neural network of human language consists of multiple and widespread regions in the whole brain. However, structural connections between

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language cortices consist of a dorsal pathway linking the superior temporal lobe and premotor cortices in the frontal lobe and a ventral pathway connecting the middle temporal lobe and the ventrolateral prefrontal cortex (Friederici, 2011). Main fiber tracts in the dorsal pathway are arcuate fascicle (AF) and superior longitudinal fascicle (SLF), while the ventral pathway includes inferior fronto-occipital fascicle (IFOF) and uncinate fascicle (UF) (Chang et al., 2015; Friederici, 2011). Additional WM tracts in language processing are inferior longitudinal fascicle (ILF) and middle longitudinal fascicle (Chang et al., 2015). Diffusion Weighted Imaging studies that focus on WM abnormalities in schizophrenia typically find an inverse relation between language functioning and fractional anisotropy (FA) in the fiber tracts in dorsal and ventral language pathways such as AF (Cavelti et al., 2018; de Boer et al., 2020; Pawełczyk et al., 2021), ILF (Rigucci et al., 2013; Viher et al., 2018; Cavelti et al., 2018; de Boer et al., 2020), IFOF (Rigucci et al., 2013; Viher et al., 2018; Cavelti et al., 2018; de Boer et al., 2020), SLF (Viher et al., 2018; Cavelti et al., 2018; de Boer et al., 2020) and UF (Viher et al., 2018; Cavelti et al., 2018; de Boer et al., 2020).

Due to the disorder's strong hereditary nature, it could be expected that first-degree family members might display similar structural brain abnormalities detected in the patients. Although language-related symptoms such as disorganized speech strongly emphasized the common genetic liability for schizophrenia supported by the studies using schizophrenia-specific polygenic risk scores and/or cortical thickness and fiber network analyses (Legge et al., 2021; Ahangari et al., 2023; Chen et al., 2023), few studies investigated possible white matter integrity abnormalities in the language-related tracts in those at familial high-risk for schizophrenia and their results are not consistent (Boos et al., 2012; Kubicki et al., 2013). In their study, Boos et al. (2012) studied some of these tracts (i.e. UF, ILF, IFOF, AF). Their results showed that siblings of young adult patients had higher mean FA in the left and right AF. With this finding, they proposed that the changes in the AF could be relevant to the risk of developing schizophrenia. In another study, Kubicki et al. (2013) found that significant decrease in axial diffusivity (AD) in AF, UF and IFOF, but not in other metrics such as FA and radial diffusivity (RD) in the siblings of patients. In other words, abnormalities in axonal rather than myelin integration, associated with the disruption in normal brain maturation, could be important to trace the language as a possible endophenotype, also known as a quantitative biological trait or biomarker, in schizophrenia (Kubicki et al., 2013).

The current study examined possible aberrations in language-related white matter tracts in patients with first-episode psychosis, their siblings and healthy controls. We hypothesized that we could see differences in these tracts in not only the first-episode psychosis patients but also in their siblings compared to the healthy controls. We employed tract-based spatial statistics (TBSS) (Smith et al., 2006) and used FA, mean diffusivity (MD), AD, and RD diffusion tensor imaging (DTI) metrics for the whole brain and the regions-of-interest (ROI) analysis. We intentionally did not use higher or lower DTI metrics value in a specific participant group in our hypothesis (e.g. lower FA value in the left AF in the siblings of FEP compared to HC) as there are limited studies and their results are inconsistent in the literature. We also assessed language by Thought and Language Index (TLI) (Liddle et al., 2002; Ulaş et al., 2007) and verbal fluency. We hypothesized that the differences in these tracts would be predicted by the scores of these language tests, so the functions of the tracts could be explained by the language ability.

2. Methods

2.1. Participants

Three groups of participants were included in the study: a first-episode psychosis group (FEP), a group who were siblings of patients with first-episode psychosis (SIB), and a healthy control group (CON). The FEP sample consisted of 20 individuals consulting to Ankara Bilkent Şehir Hospital inpatient and outpatient services. The patients were enrolled in the study when their psychiatrist determined they experienced psychosis by the Structured Clinical Interview for the DSM-V (SCID) (First, 2013). The patients were potential schizophrenia patients between the ages of 14–23 and within the first year of their psychotic break. The SIB group comprised 20 subjects who were the siblings of FEP, and their age difference with patients was a maximum of two years. The inclusion criteria of the SIB group comprised no somatic disease, no Traumatic Brain Injury (TBI), no other neurological disease, and no psychotropic drug usage (ruled out by way of self-report). The SIB group did not have any lifetime history of mental disorders, which met DSM-V criteria when they participated in the study. The CON comprised 20 subjects. They were recruited through schools, universities, and places that young people congregate such as gyms, cafes, or social media. The inclusion criteria of the CON group comprised no psychiatric history, and no family history of psychiatric illness. The exclusion criteria for all participants comprised any history of neurological or chronic somatic disorder, mental retardation, alcohol or substance abuse or dependence, or head injury. All participants were right-handed, native speakers of Turkish, and of Turkish nationality. All participants provided written informed consent. The study was approved by the Bilkent University Ethics Committee.

2.2. Measures

Thought and Language Index (TLI) is a standardized instrument developed by Liddle et al. (2002) and adapted to Turkish language by Ulaş et al. (2007) for assessing formal thought disorder. The patients are required to produce eight 1-min speech samples in response to eight black and white pictures/stimuli from Thematic Apperception Test (Murray, 1943). The speech samples are assessed according to eight types of abnormality (poverty of speech, weakening of goal, looseness, peculiar word, peculiar sentence, peculiar logic, perseveration, distractibility) which are related to positive and negative symptoms of schizophrenia. The data were scored followed the standard procedures for this task.

Verbal fluency test involves two subtypes of tests which are phonemic and semantic. Participants are asked to produce words within 1 min. In a silent room, firstly, it was expected for the participants to produce words that start with the/a, s/(Lezak, 1995) as phonemic category and secondly, words from the animal and fruit categories as semantic category. The standard procedure was followed, and necessary information was presented (i.e., please do not use the proper name and inflexional suffixes that do not change words' meaning). During the test, the errors were taken as a violation. The participants' speech was recorded via audio recorder and later transcribed for analysis. In the total word count, repetitions, synonyms, and out-of-category words were not included. Inflectional suffixes were ignored when evaluating phonemic fluency. In semantic fluency, sub-categories were only accepted as correct if the participant used both the main category and sub-category (i.e., if the participant said *fish* and then continued *anchovy*, *bass*, and *salmon*).

2.3. MRI acquisition

Images were acquired on a 3T whole body MRI scanner (Siemens Magnetom Trio; Siemens Medical Solutions, Erlangen, Germany). Radiofrequency pulses were utilized via a 32-channel SENSE head coil. Diffusion tensor imaging (DTI) measurements were acquired with a spin echo planar imaging (EPI) sequence (b-value = 1000 s/mm^2, 30 non-collinear diffusion directions; FOV read = 256 mm; flip angle = 90°; voxel size = 2 x 2 × 2 mm; slice thickness = 2 mm, 64 consecutive slices; TE = 102 ms; TR = 10740 ms) which covers the whole brain. The acquisition time was 7 min.

2.4. DTI processing

The Tract-Based Spatial Statistics (TBSS) (Smith et al., 2006), which

Table 1
Descriptive and clinical characteristics of First-Episode Psychosis (FEP) patients (n = 20), their siblings (n = 20), and healthy control group (n = 20).

	FEP Patients (n = 20)	Siblings (n = 20)	Controls (n = 20)	Test statistic	p-value
Gender					
Female	5 (25%)	10 (50%)	11 (55%)		
Male	15 (75%)	10 (50%)	9 (45%)	4.208	0.122*
Age	21 (7)	19 (6)	21 (3)	1.461	0.482**
Education (years)	12 (3)[a]	10.50 (3)[a]	14.50 (4)[b]	17.102	<0.001*
Medication (ECPZ-mg)	444.30 ± 76.79	N/A	N/A		
TLI - Total	1.88 (0.75)[a]	1 (0.69)[a]	0.50 (0.75)[b]	34.001	<0.001**
TLI - Impoverished	1.25 (0.50)[a]	1.0 (0.50)[a]	0.25 (0.50)[b]	34.028	<0.001[a]
TLI - Disorganized	0.375 (0.25)[a]	0 (0.25)[b]	0 (0.25)[b]	12.790	0.002[a]
VF - Phonemic	6.25 (5)	7.75 (3.13)	8 (4)	1.258	0.533[a]
VF - Semantic	12.75 ± 3.41[a]	14.67 ± 3.61[ab]	16.43 ± 3.88[b]	5.102	0.009[b]

Data are presented as mean ± SD or median (IQR). Categorical variables reported as frequency (percent). [a, b] Different letters indicate significant differences between the different groups ($p < 0.05$). Differences between groups were analyzed using: *Pearson chi-squared test.
[a] Kruskal-Wallis test.
[b] One-way ANOVA. ECPZ = the equivalent dose of chlorpromazine, TLI = Thought and Language Index; VF = Verbal Fluency.

is a part of the FMRIB (Functional Magnetic Resonance Imaging of the Brain's diffusion toolbox) Software Library (FSL) (http://www.fmrib.ox.ac.uk/fsl) was applied for DTI analyses. In the pre-processing of diffusion images, first, distortions and subject movements were corrected with the FSL tool "eddy" (i.e. eddy-current correction). Then, the skull was removed based on the binary brain mask by the brain extraction tool (BET). After the BET process, raw brain images were checked visually for image quality and orientation. As the final step of pre-processing, DTIFIT was utilized to fit the diffusion tensor model, and individual FA values were obtained.

In the TBSS, the fractional anisotropy (FA) image of each subject was aligned and transformed to a 1 mm × 1 mm × 1 mm Montreal Neurological Institute (MNI) 152 space via FMRIB's Non-linear Image Registration Tool (FNIRT) (Andersson et al., 2007a, 2007b). The aligned images of all subjects were merged into a single 4D image file, and the mean FA image was created by averaging all transformed data. Lastly, the mean FA image was used to generate a mean FA skeleton with a threshold of 0.2. Axial diffusivity (AD), mean diffusivity (MD) and radial diffusivity (RD) were similarly calculated. The nonlinear warps and skeleton projections of the FA images were applied to AD, MD and RD with the "non_FA" option in TBSS. For the region-of-interest analysis (ROI)-restricted TBSS analysis, ROI masks were obtained from the Johns Hopkins University (JHU) ICBM WM Tractography Atlas (Hua et al., 2009). Means and standard deviations per subject were extracted from the ROIs by masking the related parameter's skeleton with the created JHU-masks for statistical analyses.

2.5. Statistical analyses

TBSS was performed to analyze the white matter (WM) microstructure. The general linear model (GLM), rooted in non-parametric permutation test theory, was employed (Smith et al., 2006). Within the GLM framework, we conducted F-tests and t-tests. Initially, we used the F-test to check for possible significant differences in WM among the three groups. Subsequently, we applied t-tests for pairwise comparisons between groups and included age, sex, education, chlorpromazine equivalents (i.e. ECPZ, medication dose) and total intracranial volume calculated by CAT12 (Gaser et al., 2023) as variables of no interest in FSL. Variations in WM were investigated using different parameters of DTI such as FA, MD, AD, and RD. By employing a randomized tool utilizing a threshold-free cluster enhancement (TFCE) correction (Smith and Nichols, 2009), voxelwise differences in FA, MD, AD, and RD between groups were assessed with 5000 permutations (Winkler et al., 2014). In this tool, a p-value <0.05 (FWE corrected) means a statistical significance. For determining the locations of the significant clusters anatomically, the Johns Hopkins University (JHU) ICBM DTI 81 WM Labels Atlas and the JHU ICBM WM Tractography Atlas (Mazziotta et al., 2001; Wakana et al., 2007; Mori et al., 2005). In the comparisons across and between groups, means and standard deviations per subject were extracted from the ROIs by masking the related parameter's skeleton with the created JHU-masks. With these extracted values, ROI-restricted TBSS analyses were performed using the SPSS statistical package (version 23.0, Chicago, IL) and the R software (version 4.3.2, https://cran.r-project.org). One-way ANOVA and Kruskal-Wallis tests in the SPSS were used to examine whether there were differences between the three groups in terms of numerical variables. After the Kruskal-Wallis test, the Bonferroni post-hoc test was used to find out which group or groups caused the difference. The relationship between MRI findings and language tests was analyzed with Spearman's rank correlation coefficient in the R software (version 4.3.1.) because the results were not normally distributed. The correlation matrix plot was drawn using the "GGally" (Schloerke et al., 2021) package. The continuous variables were checked using probability plots and histograms. They were summarized as mean ± standard deviation (SD) when normally distributed or median (25th – 75th percentile = interquartile range, IQR) when they did not follow a normal distribution. The Kolmogorov–Smirnov test was preferred to assess the normality of data distributions. The Chi-square test was performed to analyze categorical variables. Categorical variables were presented as frequencies and percentages.

3. Results

3.1. Demographics and clinical characteristics

Demographic and clinical characteristics are summarized in Table 1. The groups did not differ in age and sex. However, they differed in education level and TLI.

3.2. Whole-brain white matter differences across groups

Using an F-test, we found significant alterations in FA, MD, AD and RD across the 3 groups in the uncinate fascicle and inferior longitudinal fascicle ($p < 0.05$, FWE corrected) (see Fig. 1 and Table 2, Table 3, Tables 4 and 5).

3.3. Whole-brain white matter differences between groups

We examined t-tests for the pairwise comparisons (e.g. FEP < CON, FEP < SIB, SIB < CON) and included age, education and sex as variables of no interest. The analysis detected significant differences of FA between SIB and CON. FA is lower in SIB than CON in UF and ILF (Fig. 2) (see Table 6).

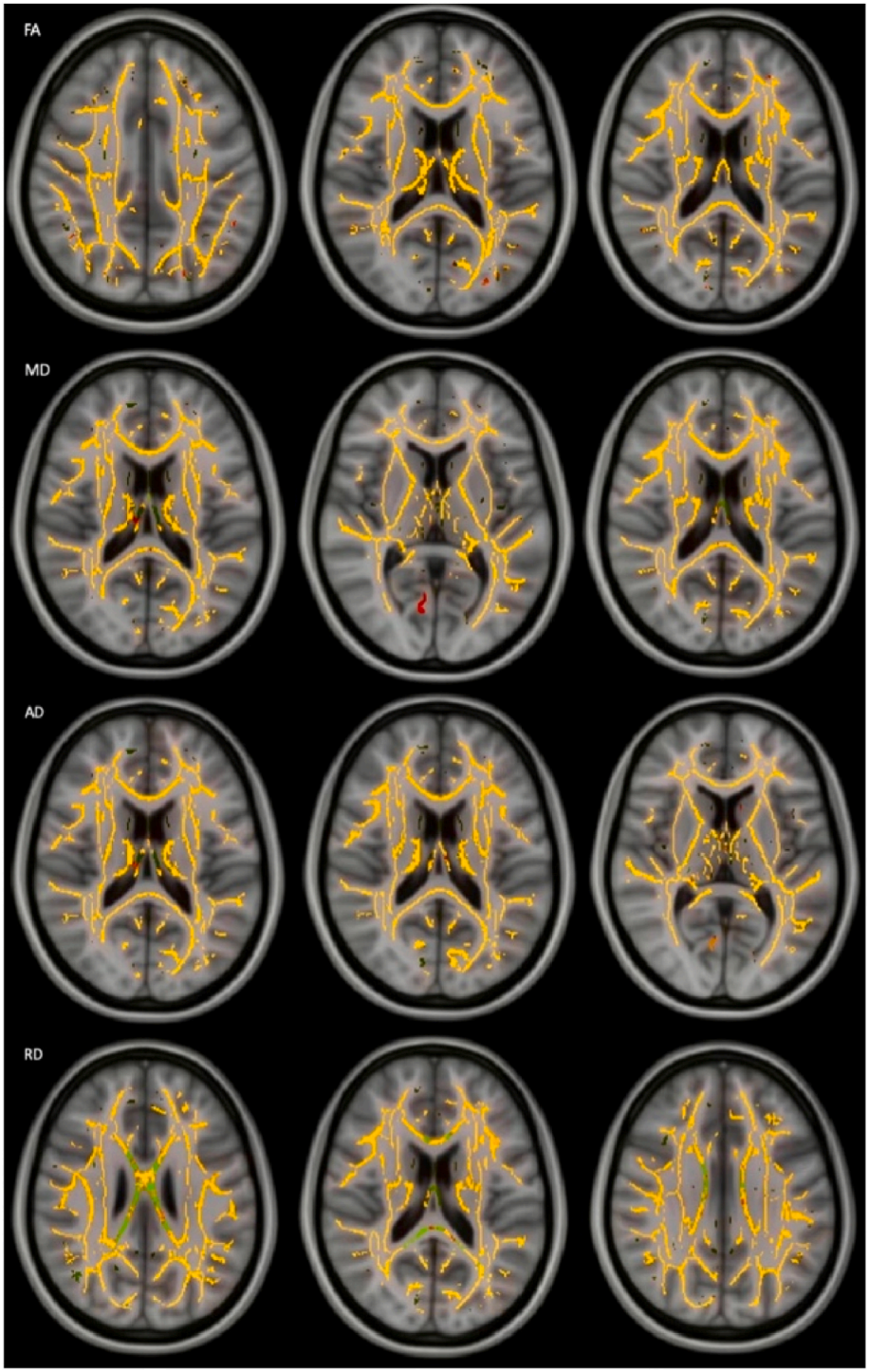

Fig. 1. The TBSS image shows WM differences (FA, MD, AD, RD) across the 3 groups (F-test). Significant clusters are indicated in red-yellow at $p < 0.05$, FWE corrected and are shown overlaid on the Montreal Neurological Institute (MNI) template and the mean FA skeleton (green).

3.4. Region-of-interest and associations of white matter with language ability

The significantly altered tracts of whole-brain analysis results were defined as ROIs (FA, MD, AD and RD of right UF and ILF). Both for across 3 groups and post-hoc pairwise comparison analyses, mean and standard deviation values per participant were extracted from each ROIs. Later, possible correlations of white matter and the language tests calculated by TLI and verbal fluency were checked (Figs. 3 and 4). Using Kruskal-Wallis, we found significant alterations in FA ($KW = 6.16$, $p = 0.046$) and RD ($KW = 6.33$, $p = 0.042$) across the 3 groups in the right UF. Among 3 groups, the reason for the alteration in the right UF (FA) ($p = 0.039$) and (RD) ($p = 0.036$) is the difference between SIB and CON. There is a positive correlation between right ILF (RD) and TLI impoverished thought/language sub-scale ($rho = 0.28$, $p < 0.05$) (Fig. 4). There was no other significant correlation between significantly differed DTI metrics (FA, MD, AD, RD) and each language test (i.e. TLI and verbal fluency) at group level.

Table 2
Location of significant differences of white matter microstructure (**FA**) across all groups.

Number of Voxels	X (mm)[a]	Y (mm)	Z (mm)	Major Tracts Included in a Cluster[b]
98579	35	9	−32	Uncinate Fasciculus R[c]: 0.04 Inferior Longitudinal Fasciculus R: 0.02

[a] MNI = Montreal Neurological Institute.
[b] Values reflect the percentage probability of the cluster to belong to the given atlas label.
[c] R = abbreviation for the right hemisphere.

Table 3
Location of significant differences of white matter microstructure (**MD**) across all groups.

Number of Voxels	X (mm)[a]	Y (mm)	Z (mm)	Major Tracts Included in a Cluster[b]
98449	35	8	−32	Uncinate Fasciculus R[c]: 0.02 Inferior Longitudinal Fasciculus R: 0.01

[a] MNI = Montreal Neurological Institute.
[b] Values reflect the percentage probability of the cluster to belong to the given atlas label.
[c] R = abbreviation for the right hemisphere.

Table 4
Location of significant differences of white matter microstructure (**AD**) across all groups.

Number of Voxels	X (mm)[a]	Y (mm)	Z (mm)	Major Tracts Included in a Cluster[b]
99578	35	8	−32	Uncinate Fasciculus R[c]: 0.02 Inferior Longitudinal Fasciculus R: 0.01

[a] MNI = Montreal Neurological Institute.
[b] Values reflect the percentage probability of the cluster to belong to the given atlas label.
[c] R = abbreviation for the right hemisphere.

Table 5
Location of significant differences of white matter microstructure (**RD**) across all groups.

Number of Voxels	X (mm)[a]	Y (mm)	Z (mm)	Major Tracts Included in a Cluster[b]
94332	35	8	−32	Uncinate Fasciculus R[c]: 0.02 Inferior Longitudinal Fasciculus R: 0.01

[a] MNI = Montreal Neurological Institute.
[b] Values reflect the percentage probability of the cluster to belong to the given atlas label.
[c] R = abbreviation for the right hemisphere.

4. Discussion

In this study, we analyzed possible differences in WM tracts in both FEP and SIB compared to the healthy controls. We expected to see these differences in language-related tracts and examined whether the aberrations in these tracts are predicted by language ability assessed with TLI and verbal fluency. As we hypothesized, we detected significant alterations in some language-related tracts among 3 groups and between SIB and CON (i.e., ILF and UF). We also proved partly their relation with the language test (i.e., TLI Impoverished thought/language sub-scale and ILF). These results also showed that the abnormalities, especially in the ILF and UF, could be taken as a possible language-related vulnerability marker in schizophrenia.

Previous studies showed that ILF and UF are in the extended language/semantic network (Catani and Bambini, 2014; Hertrich et al., 2020; Shekari and Nozari, 2023) and have related language functions. The ILF is one of the two main WM tracts with IFOF, connecting occipital lobe to the anterior regions such as temporal and frontal lobes. The UF, connecting the anterior temporal lobe to the orbitofrontal region, is taken as a major pathway of the limbic system (Catani et al., 2012). More linguistically, they are responsible for involving lexical retrieval/selection or lexical-to-semantic mapping (i.e. comprehension) and semantic-to-lexical mapping (i.e. production), semantic association, and naming (Catani et al., 2012; von der Heide et al., 2013; Harvey and Schnur, 2015; Del Tufo et al., 2019; Cocquyt et al., 2020; Surbeck et al., 2020; Jarret et al., 2022; Stein et al., 2022). However, it could be said that all these linguistic functions in these WM tracts, especially in the UF, are within the domain of the *socio-emotional* aspect of life in the extended semantic network (Von der Heide et al., 2013; Bajada et al., 2015). Language is intrinsically social. Conveying our conceptual knowledge or ideas with words to others is affected by our emotional history (Von der Heide et al., 2013). In our sample, the TLI Impoverished thought/language subscale score is relatively high. This subscale represents the features of the negative syndrome of schizophrenia (Liddle et al., 2002) and the linguistic functions of the negative symptoms are mostly reduced verbal fluency, lack of spontaneity and diminished expression of ideas during interpersonal interactions (Alpert et al., 1997; Roche et al., 2015; Kircher et al., 2018; Silva et al., 2023). Based on our results (i.e., a significant difference in UF and ILF and correlation between ILF and TLI Impoverished thought/language subscale), it could be said that not only FEP patients but also their healthy siblings are not able to talk much (e.g., *socio-emotional* aspect), so they produce fewer words and sentences compared to healthy controls.

Maderthaner et al. (2023) also found that higher Thought and Language Disorder Scale (Kircher et al., 2014) scores were associated with reduced FA in the ventral language stream (UF). In another study, Stein et al. (2022) showed a positive fiber tract association of disorganization with ILF and emphasized the role of semantic ventral stream related to linking objects to the appropriate lexical meaning (i.e., lexical access) (Herbet et al., 2018). However, in whole-brain pairwise comparison, we could not find any differences between FEP and CON in contrast to SIB and CON differences. This could be because of the medication effect in our FEP group (Duration of medication/days = M = 157.55 SD = 109.43). For example, Serpa et al. (2017) defended the beneficial effects of second-generation antipsychotics on reversing white matter abnormalities in FEP. Following the remission in all patients, significant increases in fractional anisotropy (FA) were observed in various previously affected regions, such as the IFOF, ATR, UF, and ILF (Serpa et al., 2017; Sagarwala and Nasrallah, 2021). Within this framework, lower FA in SIB, who do not use any medication, compared to CON may indicate demyelination in the language-related tracts (Cavelti et al., 2018; Viher et al., 2018). That is why this abnormality in WM tracts could be argued to reflect vulnerability to schizophrenia. As this was manifested in language-related WM tracts, it could be proposed that language ability could be a possible endophenotype in schizophrenia (Hoptman et al., 2008; Boos et al., 2013; Kubicki et al., 2013; Legge et al., 2021; Ahangari et al., 2023; Chen et al., 2023; Çabuk et al., 2023).

The limitations of our study are the following. The number of participants is relatively small. Small sample sizes do not offer enough statistical power. So, we do not know whether a lack of significance in findings accurately implies the absence of an effect or if the effect is present but too minor to be identified (Button et al., 2013). Nonetheless we have found some statistically significant differences, and the literature on FEP has been predominantly based on English speakers. This study is the first to focus on the Turkish population, providing new insights into less explored research questions. Our research protocol did not include assessments of premorbid intelligence, or standardized

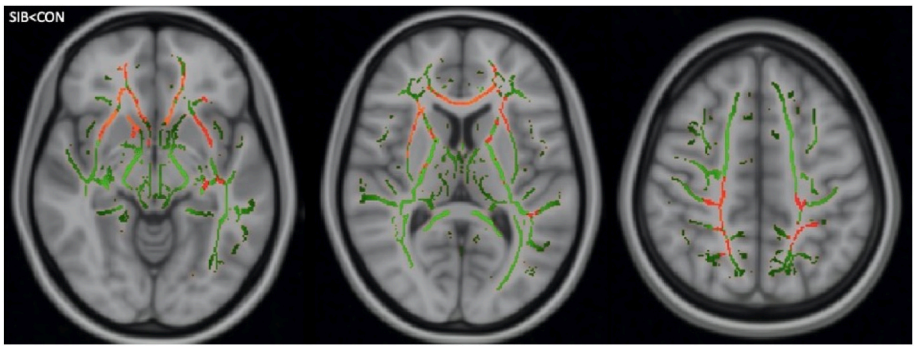

Fig. 2. The TBSS image shows lower WM integrity (FA) for siblings compared to healthy controls. Significant clusters are indicated in red-yellow at $p < 0.05$, FWE corrected and are shown overlaid on the Montreal Neurological Institute (MNI) template and the mean FA skeleton (green).

Table 6
Location of significant differences of white matter microstructure (**FA**) between siblings and healthy controls. FA is lower in siblings.

Number of Voxels	X (mm)[a]	Y (mm)	Z (mm)	Major Tracts Included in a Cluster[b]
100362	35	8	−32	Uncinate Fasciculus R: 0.02 Inferior Longitudinal Fasciculus R[c]: 0.01

[a] MNI = Montreal Neurological Institute; values reflect the percentage probability of the cluster to belong to the given atlas label.

[b] L = abbreviation for the left hemisphere, R = abbreviation for the right hemisphere.

psychiatric symptom assessments such as the Positive and Negative Syndrome Scale (Kay et al., 1987) and the Brief Psychiatric Rating Scale (Overall and Gorham, 1962). Including these assessments could have provided further insights. There was no genetic data. So, we could not analyze its mediator effect. In TBSS, voxels with the highest fractional anisotropy (FA) were mapped onto the 'skeleton'. This helped to focus the analysis on the core regions of white matter tracts but could not represent effectively the individual structural differences within the tracts (Bach et al., 2014). Although it was proven in previous studies that UF and ILF were related to verbal fluency performance (Catani et al., 2012; Powers et al., 2013; Sanvito et al., 2020; Gonzalez et al., 2021), we could not find any correlation between verbal fluency scores and the integrity of WM tracts. This could be because of our sample size.

In conclusion, the current study suggests that the presence of changes in WM among individuals with increased familial risk of developing

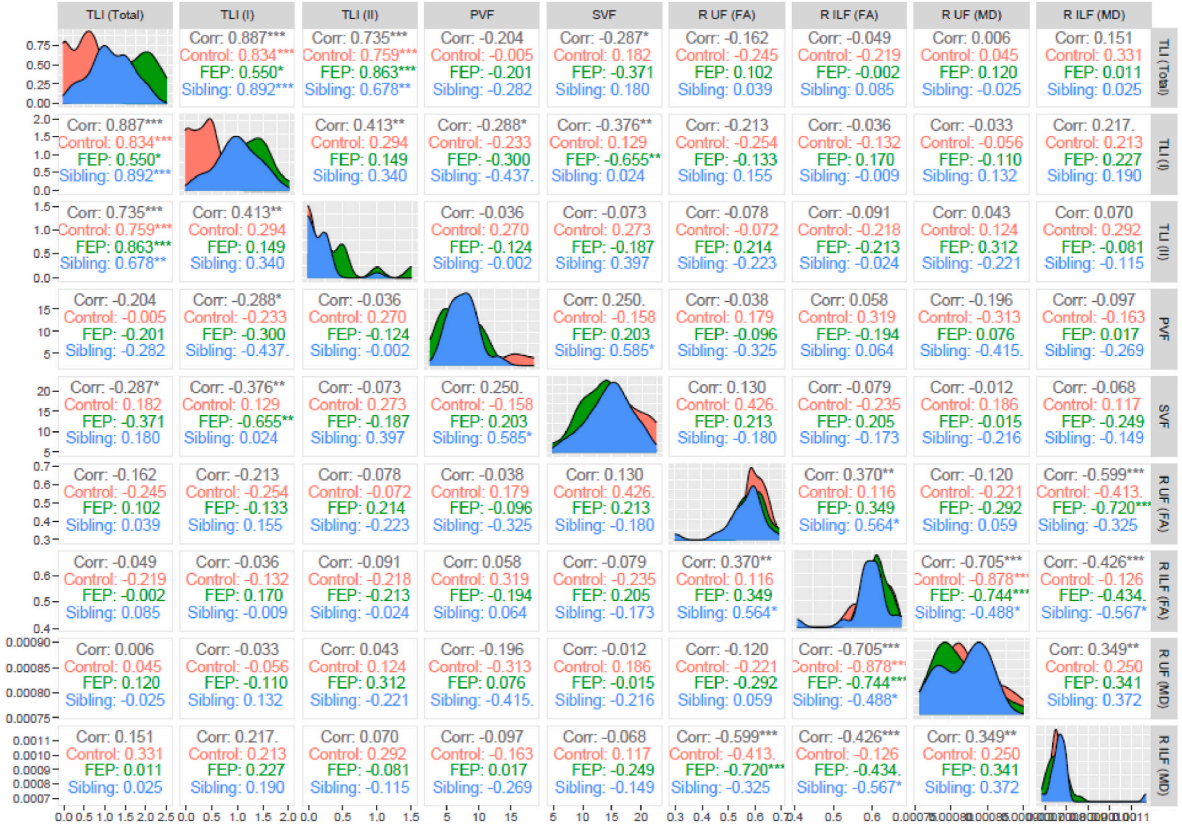

Fig. 3. Correlation matrix plot for language tests and white matter integrity (FA and MD). TLI = Thought and Language Index; TLI (I) = Thought and Language Index, Impoverished Thought and Language sub-scale; TLI (II) = Thought and Language Index, Disorganized Thought and Language sub-scale; PVF = Phonemic verbal fluency; SVF = Semantic verbal fluency. *p < 0.05; **p < 0.01; ***p < 0.001.

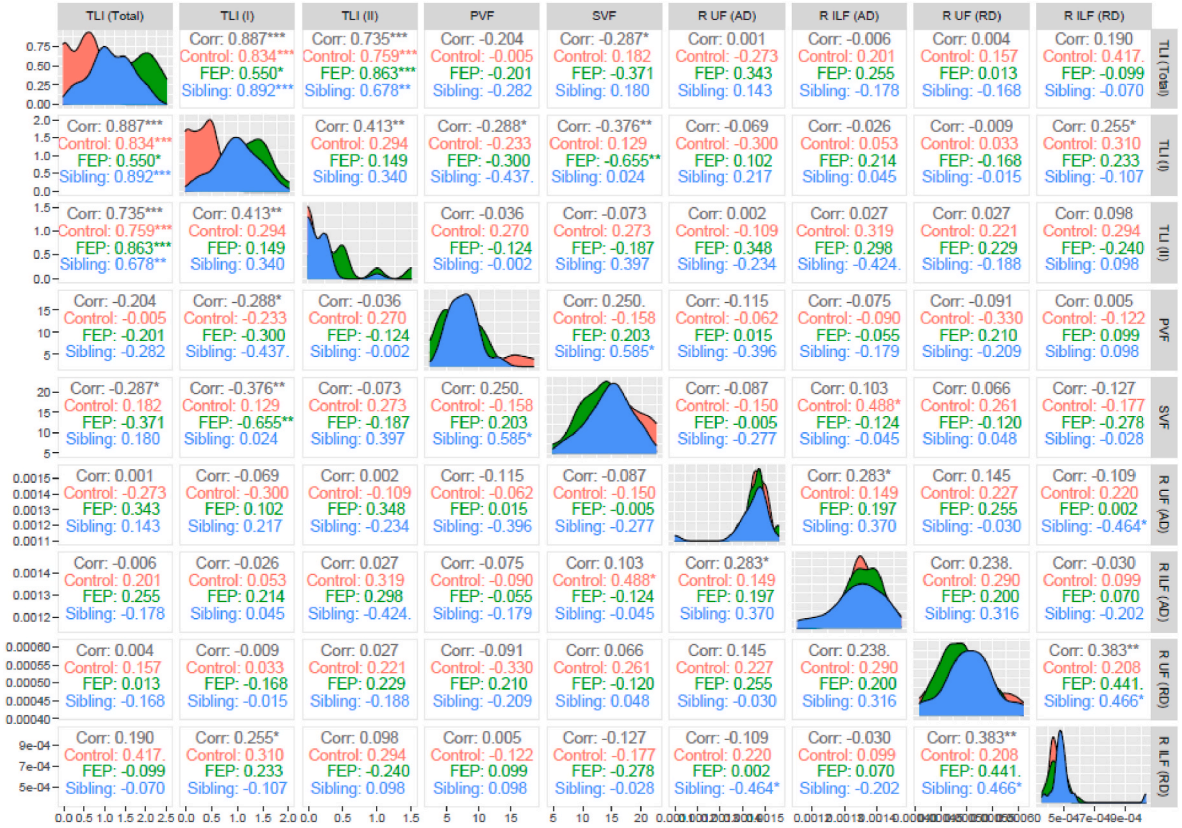

Fig. 4. Correlation matrix plot for language tests and white matter integrity (AD and RD). TLI = Thought and Language Index; TLI (I) = Thought and Language Index, Impoverished Thought and Language sub-scale; TLI (II) = Thought and Language Index, Disorganized Thought and Language sub-scale; PVF = Phonemic verbal fluency; SVF = Semantic verbal fluency. *p < 0.05; **p < 0.01; ***p < 0.001.

schizophrenia (i.e., SIB) is notable, particularly in the tracts associated with language. Also, the integrities in language-related WM tracts were predicted partly by assessing language ability with TLI and verbal fluency. Although we could not find any difference between FEP and CON because of some confounding factors such as medication effect and modest number of participants, language ability could be important in the pathophysiology of schizophrenia and could be taken as a possible vulnerability marker in schizophrenia and this could accelerate early detection, critical for a positive disease prognosis, and help to comprehend its complex pathophysiology. Further studies are required to understand better the role of language as a biomarker in schizophrenia with larger samples.

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CRediT authorship contribution statement

Tuğçe Çabuk: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Didenur Şahin Çevik:** Writing – review & editing, Investigation, Data curation. **Işık Batuhan Çakmak:** Writing – review & editing, Investigation, Data curation. **Helin Yılmaz Kafalı:** Writing – review & editing, Investigation, Data curation. **Bedirhan Şenol:** Writing – review & editing, Investigation, Data curation. **Hanife Avcı:** Writing – review & editing, Investigation, Formal analysis. **Kader Karlı Oğuz:** Writing – review & editing, Methodology, Formal analysis. **Timothea Toulopoulou:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

None of the authors has any conflicts of interest to report.

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References

Ahangari, M., Bustamante, D., Kirkpatrick, R., Nguyen, T.H., Verrelli, B.C., Fanous, A., Kendler, K.S., Webb, B.T., Bacanu, S.A., Riley, B.P., 2023. Relationship between polygenic risk scores and symptom dimensions of schizophrenia and schizotypy in multiplex families with schizophrenia. Br. J. Psychiatry 223, 301–308. https://doi.org/10.1192/bjp.2022.179.

Alpert, M., Kotsaftis, A., Pouget, E.R., 1997. At issue: speech fluency and schizophrenic negative signs. Schizophr. Bull. 23, 171–177. https://doi.org/10.1093/schbul/23.2.171.

Andersson, J.L., Jenkinson, M., Smith, S., 2007a. Non-Linear Optimisation. University of Oxford FMRIB Centre, Oxford, UK. FMRIB Technical Report TR07JA1.

Andersson, J.L., Jenkinson, M., Smith, S., 2007b. Non-linear registration. In: Aka Spatial Normalisation FMRIB Technical Report TR07JA2, 2. FMRIB Analysis Group of the University of Oxford.

Bach, M., Laun, F.B., Leemans, A., Tax, C.M.W., Biessels, G.J., Stieltjes, B., Maier-Hein, K. H., 2014. Methodological considerations on tract-based spatial statistics (TBSS). Neuroimage 100, 358–369. https://doi.org/10.1016/j.neuroimage.2014.06.021.

Bajada, C.J., Lambon Ralph, M.A., Cloutman, L.L., 2015. Transport for language south of the Sylvian fissure: the routes and history of the main tracts and stations in the ventral language network. Cortex 69, 141–151. https://doi.org/10.1016/j.cortex.2015.05.011.

Boos, H.B.M., Mandl, R.C.W., van Haren, N.E.M., Cahn, W., van Baal, G.C.M., Kahn, R.S., Hulshoff Pol, H.E., 2013. Tract-based diffusion tensor imaging in patients with schizophrenia and their non-psychotic siblings. Eur. Neuropsychopharmacol 23, 295–304. https://doi.org/10.1016/j.euroneuro.2012.05.015.

Button, K.S., Ioannidis, J.P.A., Mokrysz, C., Nosek, B.A., Flint, J., Robinson, E.S.J., Munafò, M.R., 2013. Power failure: why small sample size undermines the reliability of neuroscience. Nat. Rev. Neurosci. 14, 365–376. https://doi.org/10.1038/nrn3475.

Catani, M., Dell'Acqua, F., Vergani, F., Malik, F., Hodge, H., Roy, P., Valabregue, R., Thiebaut de Schotten, M., 2012. Short frontal lobe connections of the human brain. Cortex 48, 273–291. https://doi.org/10.1016/j.cortex.2011.12.001.

Catani, M., Bambini, V., 2014. A model for social communication And Language evolution and development (SCALED). Curr. Opin. Neurobiol. 28, 165–171. https://doi.org/10.1016/j.conb.2014.07.018.

Cavelti, M., Winkelbeiner, S., Federspiel, A., Walther, S., Stegmayer, K., Giezendanner, S., Laimböck, K., Dierks, T., Strik, W., Horn, H., Homan, P., 2018. Formal thought disorder is related to aberrations in language-related white matter tracts in patients with schizophrenia. Psychiatry Res. Neuroimaging. 279, 40–50. https://doi.org/10.1016/j.pscychresns.2018.05.011.

Chang, E.F., Raygor, K.P., Berger, M.S., 2015. Contemporary model of language organization: an overview for neurosurgeons. Journal of Neurosurgery JNS 122 (2), 250–261. https://doi.org/10.3171/2014.10.JNS132647.

Chen, X., Tan, W., Cheng, Y., Huang, D., Liu, D., Zhang, J., Li, J., Liu, Z., Pan, Y., Palaniyappan, L., 2023. Polygenic risk for schizophrenia and the language network: putative compensatory reorganization in unaffected siblings. Psychiatry Res 326, 115319. https://doi.org/10.1016/j.psychres.2023.115319.

Cocquyt, E.M., Lanckmans, E., van Mierlo, P., Duyck, W., Szmalec, A., Santens, P., De Letter, M., 2020. The white matter architecture underlying semantic processing: a systematic review. Neuropsychologia 136, 107182. https://doi.org/10.1016/j.neuropsychologia.2019.107182.

Çabuk, T., Mutlu, E., Toulopoulou, T., 2023. Thought and language disorder as a possible endophenotype in schizophrenia: evidence from patients and their unaffected siblings. Schizophr. Res. 254, 78–80. https://doi.org/10.1016/j.schres.2023.02.005.

de Boer, J.N., van Hoogdalem, M., Mandl, R.C.W., Brummelman, J., Voppel, A.E., Begemann, M.J.H., van Dellen, E., Wijnen, F.N.K., Sommer, I.E.C., 2020. Language in schizophrenia: relation with diagnosis, symptomatology and white matter tracts. npj Schizophr. 6, 1–10. https://doi.org/10.1038/s41537-020-0099-3.

Del Tufo, S.N., Earle, F.S., Cutting, L.E., 2019. The impact of expressive language development and the left inferior longitudinal fasciculus on listening and reading comprehension. J. Neurodev. Disord. 11, 1–27. https://doi.org/10.1186/s11689-019-9296-7.

First, M.B., 2013. Diagnostic and statistical manual of mental disorders, and clinical utility. J. Nerv. Ment. Dis. 201 (9), 727–729.

Friederici, A.D., 2011. The brain basis of language processing: from structure to function. Physiol. Rev. 91, 1357–1392. https://doi.org/10.1152/physrev.00006.2011.

Gaser, C., Dahnke, R., Thompson, P.M., Kurth, F., Luders, E., 2023. Cat – a computational anatomy toolbox for the analysis of structural MRI data. bioRxiv 6 (11), 495736. https://doi.org/10.1101/2022.06.11.495736, 2022.

Gonzalez, M.R., Baaré, W.F.C., Hagler, D.J., Archibald, S., Vestergaard, M., Madsen, K.S., 2021. Brain structure associations with phonemic and semantic fluency in typically-developing children. Dev. Cogn. Neurosci. 50. https://doi.org/10.1016/j.dcn.2021.100982.

Gottesman, I.I., 1991. Schizophrenia Genesis: the Origins of Madness. W H Freeman/Times Books/Henry Holt & Co.

Harvey, D.Y., Schnur, T.T., 2015. Distinct loci of lexical and semantic access deficits in aphasia: evidence from voxel-based lesion-symptom mapping and diffusion tensor imaging. Cortex 67, 37–58. https://doi.org/10.1016/j.cortex.2015.03.004.

Herbet, G., Zemmoura, I., Duffau, H., 2018. Functional anatomy of the inferior longitudinal fasciculus: from historical reports to current hypotheses. Front. Neuroanat. 12, 1–15. https://doi.org/10.3389/fnana.2018.00077.

Hertrich, I., Dietrich, S., Ackermann, H., 2020. The margins of the language network in the brain. Front. Commun. 5, 1–26. https://doi.org/10.3389/fcomm.2020.519955.

Hilker, R., Helenius, D., Fagerlund, B., Skytthe, A., Christensen, K., Werge, T.M., Nordentoft, M., Glenthøj, B., 2018. Heritability of schizophrenia and schizophrenia spectrum based on the nationwide Danish twin register. Biol. Psychiatry 83, 492–498. https://doi.org/10.1016/j.biopsych.2017.08.017.

Hoptman, M.J., Nierenberg, J., Bertisch, H.C., Catalano, D., Ardekani, B.A., Branch, C.A., DeLisi, L.E., 2008. A DTI study of white matter microstructure in individuals at high genetic risk for schizophrenia. Schizophr. Res. 106, 115–124. https://doi.org/10.1016/j.schres.2008.07.023.

Hua, K., Oishi, K., Zhang, J., Wakana, S., Yoshioka, T., Zhang, W., Akhter, K.D., Li, X., Huang, H., Jiang, H., Van Zijl, P., Mori, S., 2009. Mapping of functional areas in the human cortex based on connectivity through association fibers. Cereb. Cortex 19, 1889–1895. https://doi.org/10.1093/cercor/bhn215.

Jarret, J., Ferré, P., Chedid, G., Bedetti, C., Bore, A., Joanette, Y., Rouleau, I., Maria Brambati, S., 2022. Functional network and structural connections involved in picture naming. Brain Lang. 231. https://doi.org/10.1016/j.bandl.2022.105146.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13 (2), 261–276.

Kircher, T., Krug, A., Stratmann, M., Ghazi, S., Schales, C., Frauenheim, M., Turner, L., Fährmann, P., Hornig, T., Katzev, M., Grosvald, M., Müller-Isberner, R., Nagels, A., 2014. A rating scale for the assessment of objective and subjective formal thought and language disorder (TALD). Schizophr. Res. 160, 216–221. https://doi.org/10.1016/j.schres.2014.10.024.

Kircher, T., Bröhl, H., Meier, F., Engelen, J., 2018. Formal thought disorders: from phenomenology to neurobiology. Lancet Psychiatr. 5 (6), 515–526. https://doi.org/10.1016/S2215-0366(18)30059-2.

Kubicki, M., Shenton, M.E., Maciejewski, P.K., Pelavin, P.E., Hawley, K.J., Ballinger, T., Swisher, T., Jabbar, G.A., Thermenos, H.W., Keshavan, M.S., Seidman, L.J., DeLisi, L. E., 2013. Decreased axial diffusivity within language connections: a possible biomarker of schizophrenia risk. Schizophr. Res. 148, 67–73. https://doi.org/10.1016/j.schres.2013.06.014.Decreased.

Legge, S.E., Cardno, A.G., Allardyce, J., Dennison, C., Hubbard, L., Pardiñas, A.F., Richards, A., Rees, E., Di Florio, A., Escott-Price, V., Zammit, S., Holmans, P., Owen, M.J., O'Donovan, M.C., Walters, J.T.R., 2021. Associations between schizophrenia polygenic liability, symptom dimensions, and cognitive ability in schizophrenia. JAMA Psychiatr. 78, 1143–1151. https://doi.org/10.1001/jamapsychiatry.2021.1961.

Lezak, M.D., 1995. Neuropsychological Assessment, third ed. Oxford University Press.

Lichtenstein, P., Yip, B.H., Björk, C., Pawitan, Y., Cannon, T.D., Sullivan, P.F., Hultman, C.M., 2009. Common genetic influences for schizophrenia and bipolar disorder: a population-based study of 2 million nuclear families. Lancet 373, 1–14. https://doi.org/10.1016/S0140-6736(09)60072-6.Common.

Liddle, P.F., Ngan, E.T.C., Caissie, S.L., Anderson, C.M., Bates, A.T., Quested, D.J., White, R., Weg, R., 2002. Thought and language index: an instrument for assessing thought and language in schizophrenia. Br. J. Psychiatry 181, 326–330. https://doi.org/10.1192/bjp.181.4.326.

Maderthaner, L., Pavlidou, A., Lefebvre, S., Nadesalingam, N., Chapellier, V., Von Känel, S., Kyrou, A., Alexaki, D., Wüthrich, F., Weiss, F., Baumann-Gama, D., Wiest, R., Strik, W., Kircher, T., Walther, S., 2023. Neural correlates of formal thought disorder dimensions in psychosis. Schizophr. Bull. 49, S104–S114. https://doi.org/10.1093/schbul/sbac120.

Mori, S., Wakana, S., Nagae-Poetscher, L.M., van Zijl, P.C., 2005. MRI Atlas of Human White Matter. Elsevier, Amsterdam, The Netherlands.

Murray, H., 1943. Manual for the Thematic Apperception Test. Harvard University Press, Cambridge, MA.

Overall, J.E., Gorham, D.R., 1962. The Brief psychiatric rating scale. Psychol. Rep. 10, 799–812.

Pawełczyk, A., Łojek, E., Żurner, N., Gawłowska-Sawosz, M., Gębski, P., Pawełczyk, T., 2021. The correlation between white matter integrity and pragmatic language processing in first episode schizophrenia. Brain Imaging Behav 15, 1068–1084. https://doi.org/10.1007/s11682-020-00314-6.

Powers, J.P., McMillan, C.T., Brun, C.C., Yushkevich, P.A., Zhang, H., Gee, J.C., Grossman, M., 2013. White matter disease correlates with lexical retrieval deficits in primary progressive aphasia. Front. Neurol. 4 DEC, 1–9. https://doi.org/10.3389/fneur.2013.00212.

Rigucci, S., Rossi-Espagnet, C., Ferracuti, S., De Carolis, A., Corigliano, V., Carducci, F., Mancinelli, I., Cicone, F., Tatarelli, R., Bozzao, A., Girardi, P., Comparelli, A., 2013. Anatomical substrates of cognitive and clinical dimensions in first episode schizophrenia. Acta Psychiatr. Scand. 128, 261–270. https://doi.org/10.1111/acps.12051.

Roche, E., Creed, L., Macmahon, D., Brennan, D., Clarke, M., 2015. The epidemiology and associated phenomenology of formal thought disorder: a systematic review. Schizophr. Bull. 41, 951–962. https://doi.org/10.1093/schbul/sbu129.

Sagarwala, R., Nasrallah, H.A., 2021. The effect of antipsychotic medications on white matter integrity in first-episode drug-naïve patients with psychosis: a review of DTI studies. Asian J. Psychiatr. 61, 102688. https://doi.org/10.1016/j.ajp.2021.102688.

Sanvito, F., Caverzasi, E., Riva, M., Jordan, K.M., Blasi, V., Scifo, P., Iadanza, A., Crespi, S.A., Cirillo, S., Casarotti, A., Leonetti, A., Puglisi, G., Grimaldi, M., Bello, L., Gorno-Tempini, M.L., Henry, R.G., Falini, A., Castellano, A., 2020. fMRI-targeted high-angular resolution diffusion MR tractography to identify functional language tracts in healthy controls and glioma patients. Front. Neurosci. 14, 1–17. https://doi.org/10.3389/fnins.2020.00225.

Schloerke, Barret, Cook, Di, Larmarange, Joseph, Briatte, Francois, Marbach, Moritz, Thoen, Edwin, Elberg, Amos, Crowley, Jason, 2021. GGally: extension to Ggplot2. https://CRAN.R-project.org/package=GGally.

Serpa, M.H., Doshi, J., Erus, G., Chaim-Avancini, T.M., Cavallet, M., Van De Bilt, M.T., Sallet, P.C., Gattaz, W.F., Davatzikos, C., Busatto, G.F., Zanetti, M.V., 2017. State-dependent microstructural white matter changes in drug-naïve patients with first-episode psychosis. Psychol. Med. 47, 2613–2627. https://doi.org/10.1017/S0033291717001015.

Shekari, E., Nozari, N., 2023. A narrative review of the anatomy and function of the white matter tracts in language production and comprehension. Front. Hum. Neurosci. 17, 1–41. https://doi.org/10.3389/fnhum.2023.1139292.

Silva, A.M., Limongi, R., MacKinley, M., Ford, S.D., Alonso-Sánchez, M.F., Palaniyappan, L., 2023. Syntactic complexity of spoken language in the diagnosis of schizophrenia: a probabilistic Bayes network model. Schizophr. Res. 259, 88–96. https://doi.org/10.1016/j.schres.2022.06.011.

Smith, S.M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T.E., Mackay, C.E., Watkins, K.E., Ciccarelli, O., Cader, M.Z., Matthews, P.M., Behrens, T.E.J., 2006. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. Neuroimage 31, 1487–1505. https://doi.org/10.1016/j.neuroimage.2006.02.024.

Smith, S.M., Nichols, T.E., 2009. Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. Neuroimage 44, 83–98. https://doi.org/10.1016/j.neuroimage.2008.03.061.

Stein, F., Buckenmayer, E., Brosch, K., Meller, T., Schmitt, S., Ringwald, K.G., Pfarr, J.K., Steinsträter, O., Enneking, V., Grotegerd, D., Heindel, W., Meinert, S., Leehr, E.J., Lemke, H., Thiel, K., Waltemate, L., Winter, A., Hahn, T., Dannlowski, U., Jansen, A., Nenadić, I., Krug, A., Kircher, T., 2022. Dimensions of formal thought disorder and their relation to gray- and white matter brain structure in affective and psychotic disorders. Schizophr. Bull. 48, 902–911. https://doi.org/10.1093/schbul/sbac002.

Surbeck, W., Hänggi, J., Scholtes, F., Viher, P.V., Schmidt, A., Stegmayer, K., Studerus, E., Lang, U.E., Riecher-Rössler, A., Strik, W., Seifritz, E., Borgwardt, S., Quednow, B.B., Walther, S., 2020. Anatomical integrity within the inferior fronto-occipital fasciculus and semantic processing deficits in schizophrenia spectrum

disorders. Schizophr. Res. 218, 267–275. https://doi.org/10.1016/j.schres.2019.12.025.

Ulaş, H., Alptekin, K., Özbay, D., Akdede, B.B., Çakir, E., Tümüklü, M., Şimşek, S., Arkar, H., Akvardar, Y., 2007. Düşünce ve dil ölçeğinin türkçe formunun geçerlilik ve güvenilirlik çalişmasi. Klin. Psikiyatr 77–85.

Viher, P.V., Stegmayer, K., Giezendanner, S., Federspiel, A., Bohlhalter, S., Wiest, R., Strik, W., Walther, S., 2018. White matter correlates of the disorganized speech dimension in schizophrenia. Eur. Arch. Psychiatry Clin. Neurosci. 268, 99–104. https://doi.org/10.1007/s00406-016-0753-y.

Von Der Heide, R.J., Skipper, L.M., Klobusicky, E., Olson, I.R., 2013. Dissecting the uncinate fasciculus: disorders, controversies and a hypothesis. Brain 136, 1692–1707. https://doi.org/10.1093/brain/awt094.

Wakana, S., Caprihan, A., Panzenboeck, M.M., Fallon, J.H., Perry, M., Gollub, R.L., Hua, K., Zhang, J., Jiang, H., Dubey, P., Blitz, A., van Zijl, P., Mori, S., 2007. Reproducibility of quantitative tractography methods applied to cerebral white matter. Neuroimage 36, 630–644. https://doi.org/10.1016/j.neuroimage.2007.02.049.

Winkler, A.M., Ridgway, G.R., Webster, M.A., Smith, S.M., Nichols, T.E., 2014. Permutation inference for the general linear model. NeuroImage 92, 381–397. https://doi.org/10.1016/j.neuroimage.2014.01.060.

Zimmerer, V.C., Watson, S., Turkington, D., Ferrier, I.N., Hinzen, W., 2017. Deictic and propositional meaning-New perspectives on language in Schizophrenia. Front. Psychiatry 8, 15–19. https://doi.org/10.3389/fpsyt.2017.00017.