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SEX DIFFERENCES IN THE CONNECTOME OF THE HUMAN BRAIN ACCORDING TO AN MR-TRACTOGRAPHY STUDY

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Background: *The gender differences in the brain anatomy play an important role in planning and analysis in a lot of studies of the brain. Despite most animal studies being performed on the animals of only one sex, clinical studies generally enroll both males and females. Keeping this fact in mind, learning the gender differences in the white matter structure is important for those studies which deal with the white matter changes. These differences should be considered on the stages of planning and evaluation of the results.* ***Aims:*** *Evaluation of the gender differences in the white matter pathways in healthy subjects.* ***Methods:*** *21 women and 20 men were enrolled in the study. All the subjects underwent MR-tractography, then the anatomic connectome was composed and the differences were evaluated using the tracts quantitative anisotropy (QA) evaluation.* ***Results:*** *The gender differences were found in the white matter pathways with the prevalence of quantitative anisotropy in women, observed in a larger number of tracts than in those of men. QA was prevalent in a lot of fascicli that form major pathways in both groups: corpus callosum, dominant arcuate fasciclus, inferior fronto-occipital, inferior and superior right longitudinal pathways.* ***Conclusions:*** *The white matter pathways in males and females are different not only within the major tracts but also for small fascicli that form tracts.*

Keywords: *connectome; healthy volunteers; sex characteristics; MR-tractography.*

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BACKGROUND

The identification of sex differences in brain structures in the light of rapidly developing neuroscience becomes increasingly important annually in planning experiments and subsequent evaluation of results [1]. For example, for some psychiatric diseases, sex-related clinical and epidemiological aspects are noted [2, 3]. By contrast, in psychology, the hypothesis of sex similarity is still dominant in research [4]; however, it is often supplemented by data with certain variability [5]. Structural analysis of the human brain demonstrated a difference not only in the volume and thickness of the cortex of some brain areas but also in the size of the major white matter pathways [6].

Brain researchers' attention is riveted to the relatively new concept of the connectome, which is a complete description of the connections in the nervous system. At the anatomical level, the connectome can be assessed using magnetic resonance tractography when constructing pathways [7].

In this study, we assessed the sex difference in the conduction tracts in the brain (except the cerebellum) of men and women according to magnetic resonance imaging (MRI) tractography without the initial identification of major white matter tracts. The anatomical localization of the changes identified was determined by using a specialized atlas for MR tractography.

We used the quantitative anisotropy (QA) index that characterizes the difference in the properties of the environment along the conducting path, and the higher this index, the more co-directed the conducting paths, and conversely, the lower the index, the more chaotic their direction within the studied volume [8].

This study aimed to evaluate the sex differences in the conduction pathways of the white matter in a healthy brain.

METHODS

Study design

The study enrolled healthy volunteers (*n*=41) who underwent preliminary selection, including examination by medical specialists and several instrumental studies to rule out general somatic pathology and pathology of the central nervous system (CNS). All participants underwent MRI tractography, and its results were used to reconstruct links within the white matter of the brain. Then, two study groups of volunteers were formed according to sex (women, *n*=21; men, *n*=20), and the differences in the QA index of the reconstructed brain pathways between the study groups were assessed.

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Eligibility criteria

At the selection stage, each participant was examined by a therapist, neurologist, and psychiatrist (collection of complaints and anamnesis, therapeutic examination, assessment of neurological and mental states, respectively) to rule out possible somatic and mental pathology.

In addition, several instrumental studies were performed to rule out possible general somatic and CNS pathologies, which consisted of electroencephalography, duplex scanning of the brachiocephalic arteries, transcranial duplex scanning, transthoracic echocardiography, and structural MRI with time-of-flight MR angiography of the brain.

The *inclusion criteria* were age 18–80 years, Russian as the native language, and intact consciousness.

The *exclusion criteria* were a history of serious CNS diseases (such as stroke, epilepsy, tumor, aneurysm, and intracranial or spinal cord surgery), pregnancy, oncological history, major surgery or major injury in the last 12 months, behavioral and consciousness impairment, somatic diseases in the stage of decompensation, history of mental illness, intake of psychotropic agents at the time of examination, addiction to psychoactive drugs, MRI contraindications, poor quality of MR images, signs of intracranial micro- and macrohemorrhage according to MRI, and any other CNS pathologies identified during to the study, withdrawal of the consent to participate, and lack of communication (control) with the patient.

Study conditions

All studies were conducted at the Federal Center of Brain and Neurotechnologies of the Federal Medical and Biological Agency of Russia voluntarily. No material and financial rewards and/or other incentives were provided to volunteers.

Study duration

The enrollment of volunteers was conducted from June to December 2021.

Research methodology

All studies were performed on a Discovery MR750w Magnetic Resonance Tomograph (GE Healthcare, USA) with a magnetic field induction of 3.0 T using a 32-channel head coil. To study brain white matter pathways, a diffusion-weighted echo-planar pulse sequence was used with the following parameters: time of echo, 91.7 ms; time of repetition, 10559 ms; diffusion directions, 64; b-value, 1500 s/mm^2; and voxel size, 2.5×2.5×2.5 mm. Further data processing was performed using the DSI-Studio software package (dsi-studio.labsolver.org).

At the stage of primary data processing, the shift along the brain boundaries caused by artifacts of magnetic susceptibility was compensated using an additional diffusion-weighted echo-planar pulse sequence with a 180° phase-coding gradient (compared with the main series). Data were then reconstructed in the normalized Montreal Neurological Institute (MNI) coordinate system using q-space deformable reconstruction (QSDR) [9], diffusion sampling length ratio of 1.25, and final resolution after reconstruction of 2×2×2 mm.

Statistical analysis between the male and female groups for the brain pathways constructed in this way was performed using nonparametric Spearman correlation, the T-score cutoff level was set to 2.5, and a deterministic tract tracing algorithm was chosen [10].

QA was used to search for pathways in the entire brain, except for the cerebellum. The resulting array of pathways was filtered using an atlas based on data from the Human Connectome Project, created with the involvement of 1065 volunteers [11] in 33 iterations. To highlight the differences in the conduction pathways of the brain between the study groups, a correction for multiple comparisons (false discovery rate correction) with a p=0.05 level was applied. The minimum length of the reconstructed tracts was 10 voxels (20 mm).

Ethical considerations

The study was approved by the local ethics committee of the Federal Center of Brain and Neurotechnologies of the Federal Medical and Biological Agency of Russia (May 17, 2021).

Statistical analysis

The sample size was not preliminarily calculated, and the main factor was the throughput of the center to perform all studies in the selection for the main experiment with an equal number of participants in each group.

Data and statistical analyses were performed using the DSI-Studio software package. Spearman's nonparametric correlation was used for the reconstructed pathways in both groups, adjusted for multiple comparisons and at a significance level of 0.05.

RESULTS

Study participants

A total of 41 patients were enrolled in the study, including 21 (51.2%) women and 20 (48.8%) men. The median age of the female group was 29 [26–35] years

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and that of the male group was 34 [26; 38] years. Most of the participants (*n*=39) were right-handed, and 1 man and 1 woman were left-handed.

Primary results

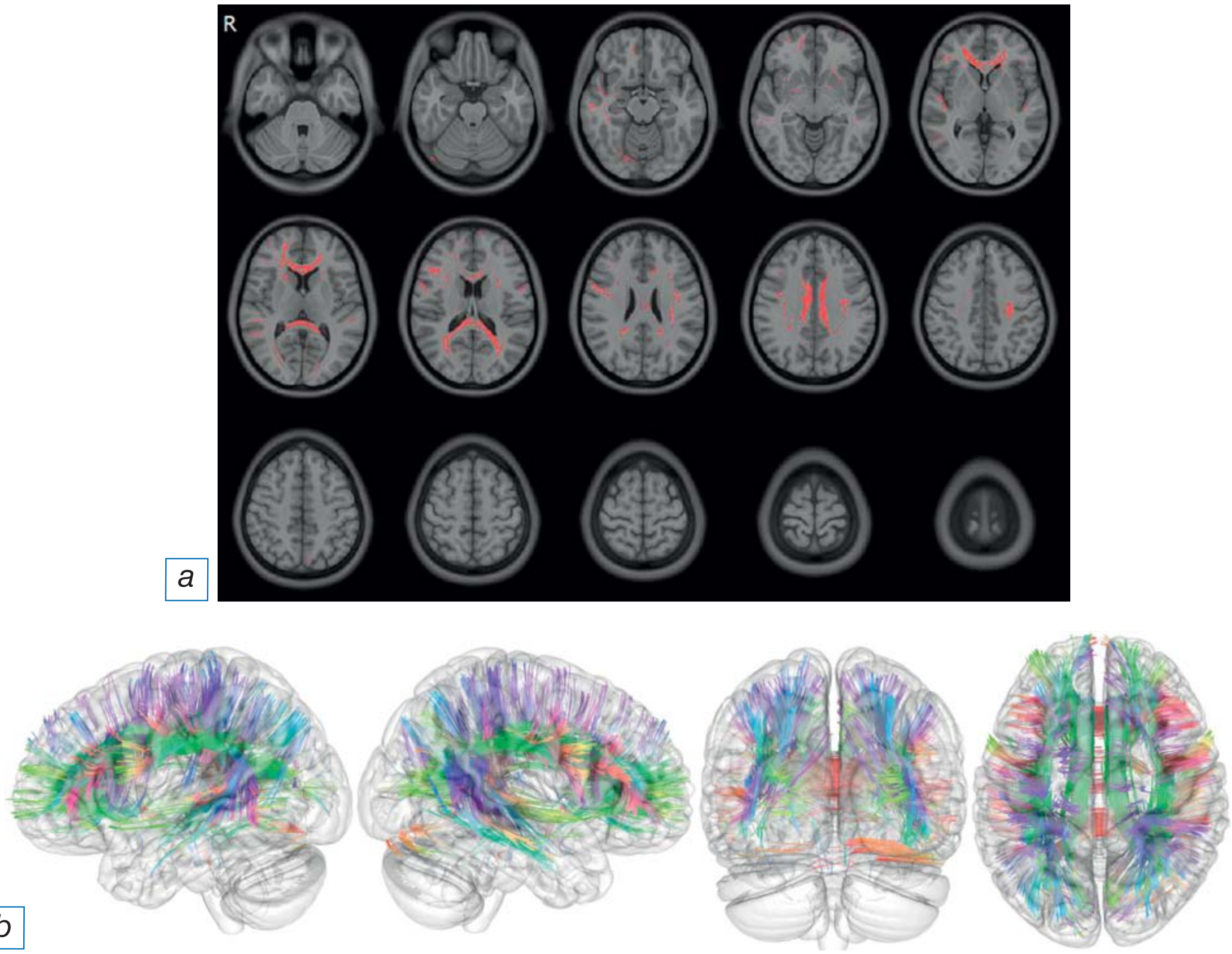
All MR tractography data were reconstructed using the QSDR algorithm, which included data normalization in the MNI space, which leveled out the difference in the volume of different brain regions in volunteers. The white matter conduction system of the brain, except the cerebellum, was then reconstructed, and QA analysis was performed along each reconstructed tract. Statistical evaluation in the study groups was performed for each tract and adjusted for multiple comparisons. The results of the analysis were presented as reconstructions in different colors. Figure 1 presents the tracts with the highest QA for men, and Figure 2 presents those for women.

When the results obtained were superimposed in the same volume, the overlap of some of the identified conducting pathways of the white matter was noticeable; moreover, differences were also revealed. The results are presented in Fig. 3.

Visual evaluation of data is difficult because of the large number of reconstructed tracts. In this regard, in addition to the visual representation, an automatic classification of all identified differences was made according to the tractographic atlas HCP842 [12]. The findings are presented in Table 1.

As shown in Table 1, similar brain pathways were classified with a predominant indicator of QA. For these pathways (an example is shown in Fig. 4), some of the fascicles constituting them have large QA values in men, and some of the fascicles have large QA values in women. When classifying, they were assigned to the same anatomical tract or part of it. In addition, the HCP842 tractographic atlas highlights different fascicles of the same anatomical tract, which enables identifying this difference for some of them.

a



b

Fig. 1. MR tomograms (*a*) and 3D reconstructions (*b*) of the brain in various projections with the marked pathways, characterized by a higher index of quantitative anisotropy (QA), in men. The spatial direction of the revealed tracts is highlighted in color in panel (*b*).

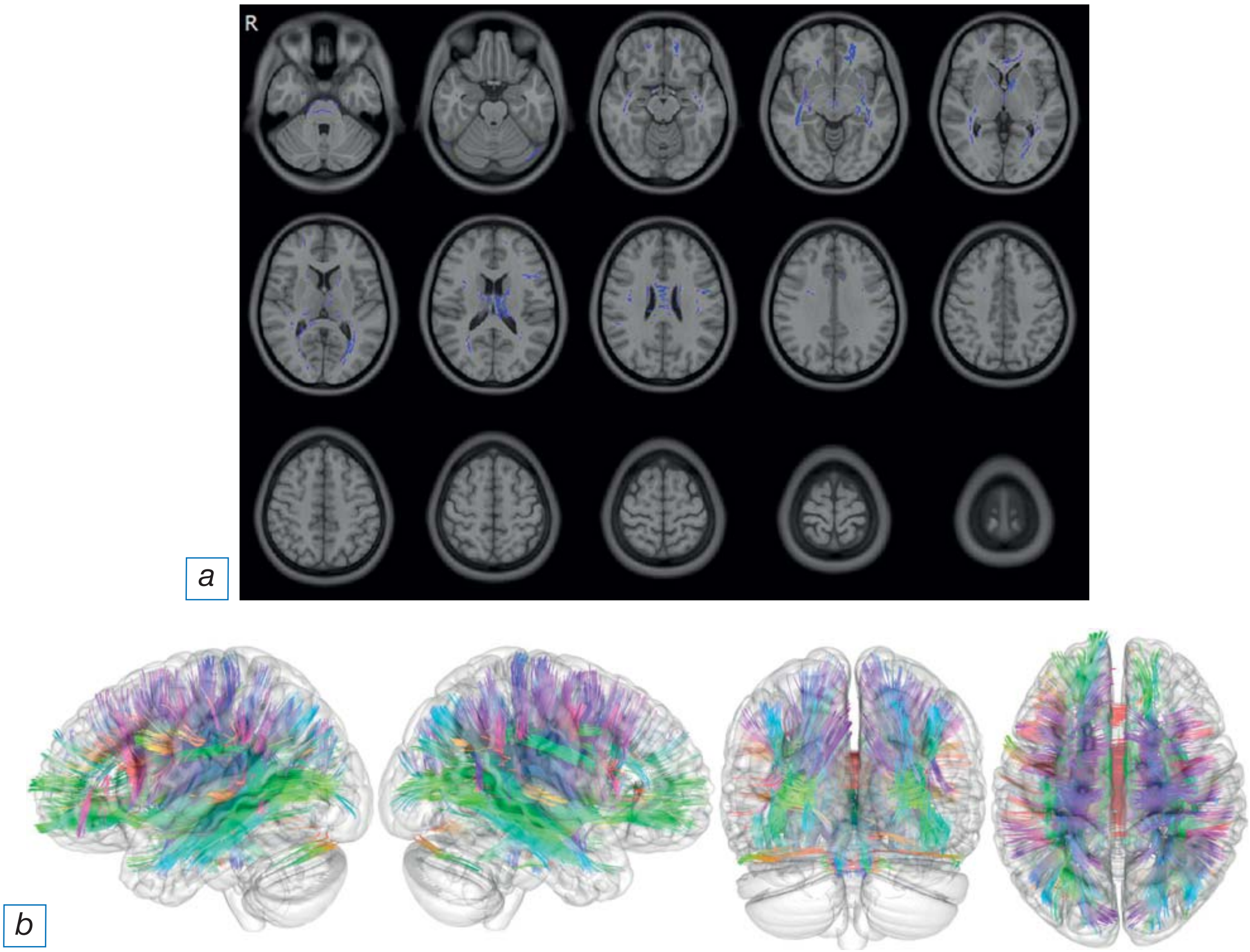


Fig. 2. MR tomograms (*a*) and 3D reconstructions (*b*) of the brain in various projections with the marked pathways, characterized by a higher index of quantitative anisotropy (QA), in women. The spatial direction of the revealed tracts is highlighted in color in panel (*b*).

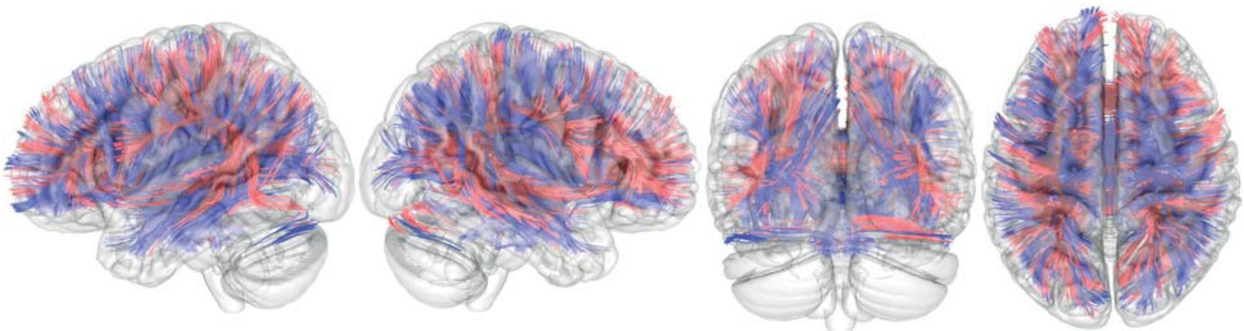


Fig. 3. 3D reconstructions of the brain and pathways with the highest index of quantitative anisotropy (QA), in men (red) and women (blue).

In the male group, the pathways of the nondominant arcuate fascicle on the right prevailed (most of the participants were right-handed), as well as the cingulate gyrus tracts, anterior sections of the cortical-striatal tract, reticular tract on the right, and part of the superior longitudinal fasciculus on the left and right.

In the female group, a predominance of the following tracts was noted: conduction tracts of the anterior commissure, part of the cingulate gyrus tract in the parahippocampal region on the left, corticopontine tract in the frontal and occipital lobes on the right, corticopontine tract of the parietal lobe on

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Table 1

Arrays of tracts obtained as a result of automatic calculation that have a statistically significantly higher QA for groups of men and women

Men	Women
Arcuate Fasciculus L Corpus Callosum Body Corpus Callosum Forceps Major Corpus Callosum Forceps Minor Corpus Callosum Tapetum Inferior Fronto Occipital Fasciculus L Inferior Fronto Occipital Fasciculus R Inferior Longitudinal Fasciculus R Superior Longitudinal Fasciculus2 R	Arcuate Fasciculus L Corpus Callosum Body Corpus Callosum Forceps Major Corpus Callosum Forceps Minor Corpus Callosum Tapetum Inferior Fronto Occipital Fasciculus L Inferior Fronto Occipital Fasciculus R Inferior Longitudinal Fasciculus R Superior Longitudinal Fasciculus2 R
Arcuate Fasciculus R Cingulum Frontal Parahippocampal L Cingulum Frontal Parietal L Cingulum Frontal Parietal R Cingulum Rarolfactory L Cingulum Rarolfactory R Corticostriatal Tract Anterior L Corticostriatal Tract Anterior R Reticular Tract R Superior Longitudinal Fasciculus1 L Superior Longitudinal Fasciculus2 L Superior Longitudinal Fasciculus3 R	Anterior Commissure Cingulum Parahippocampal Parietal L Corticopontine Tract Frontal R Corticopontine Tract Occipital R Corticopontine Tract Parietal L Corticopontine Tract Parietal R Corticospinal Tract L Corticospinal Tract R Corticostriatal Tract Posterior L Corticostriatal Tract Posterior R Corticostriatal Tract Superior L Corticostriatal Tract Superior R Dentatorubrothalamic Tract L Dentatorubrothalamic Tract R Extreme Capsule L Fornix L Fornix R Frontal Aslant Tract L Inferior Longitudinal Fasciculus L Medial Lemniscus R Optic Radiation L Thalamic Radiation Anterior L Thalamic Radiation Anterior R Thalamic Radiation Posterior L Thalamic Radiation Superior L Thalamic Radiation Superior R

both sides, pyramidal tract on both sides, posterior and upper parts of the corticostriatal tract, dentato-rubro-thalamic tract on both sides, outermost capsule on the left, pathways of the fornix on both sides, frontal oblique tract on the left, lower longitudinal fascicle on the left, medial lemniscus on the right, optic radiation on the left, superior and anterior thalamocortical tract, and posterior thalamocortical tract path on the left.

Within one anatomical tract, the predominance of its various fascicles was noted in both sexes, namely, the dominant arcuate tract on the left (most of the participants were right-handed), pathways of the corpus callosum, lower fronto-occipital fascicle, and lower and upper longitudinal fascicles on the right.

DISCUSSION

The results of the study suggest the existence of sex differences in the conduction system of the human brain. In addition to the revealed differences in large anatomical tracts, a difference was detected in the fascicles forming them. These differences were manifested in both the classification of fascicles with high QA values (different parts of the same conductive path turned out to be typical for both sexes) and overlap of results during automatic classification using the HCP842 tractographic atlas.

The findings revealed an overlap in the predominance of the QA index of individual tract fascicles within one anatomical pathway. If similar tracts were ipsilaterally excluded from the data, then for men, only

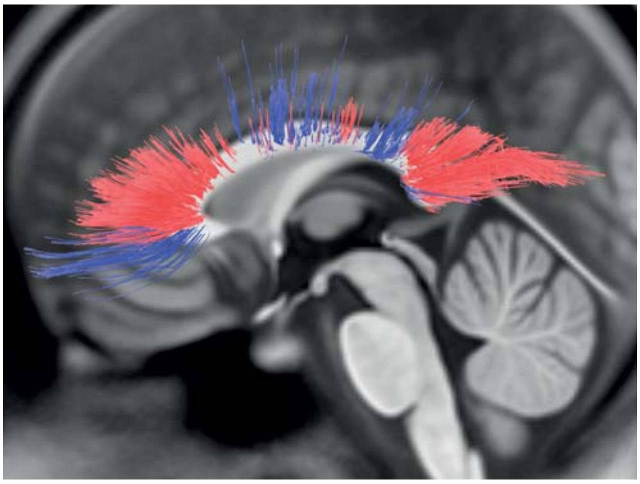

Fig. 4. 3D visualization of the pathways of the corpus callosum with the highest index of quantitative anisotropy (QA), in men (red) and women (blue). The tracts prevailing for the two sexes, are displayed, which pass through different parts and fascicle of the corpus callosum.

the right-sided predominance of the nondominant arcuate fascicle, cingulate gyrus tracts, and reticular tract was noted. Moreover, for women, the bilateral predominance of the anterior commissure, corticopontine tract, pyramidal tract, dentato-rubro-thalamic tract, conducting tracts of the fornix, and thalamocortical tract is more extensively represented. In addition, women showed ipsilateral predominance of the outermost capsule on the left, frontal oblique tract on the left, optic radiation on the left, and medial lemniscus on the right.

In a study of sex differences in a large sample of 5216 volunteers, Ritchie et al. [6] revealed a difference in fractional anisotropy (FA), which turned out to be in the pyramidal tract, and acoustic radiation in men, and women have a more pronounced scatter in the FA values of the pyramidal tract than men. The authors noted the possible contribution of "partial averaging" in the assessment of FA; thus, the data analysis was performed using 22 major tracts of the brain conduction system selected in advance.

In the present study, all brain pathways were first reconstructed and then classified using a tractographic atlas. In addition, QA was used instead of FA. The chosen indicator characterizes the anisotropy of the diffusion of water molecules along the chosen direction (along the course of the chosen fascicle of the conducting pathway of the white matter) and not entirely in the voxel under study. With such a calculation, the information obtained was more related to the studied tract, rather than the voxel position in the brain substance, thereby reducing the contribution of "partial" averaging when crossing the conducting pathways [8].

Jung et al. [13] enrolled 72 volunteers and found large FA values in the conduction tracts, namely, left anterior thalamocortical, right girdle-angular, right pyramidal, temporal ending of the upper longitudinal on both sides, uncinate on both sides, and forceps frontalis of the corpus callosum in men. Moreover, in women, there was a predominance of radial diffusivity (RD) in the left anterior, thalamocortical, and left uncinate conducting pathways. RD is one of the indices of diffusion tensor tomography, one of the first methods of tractography, which also includes the FA; as a result, RD is also subject to "partial averaging."

In a study by Kanaan et al. [14], with a sample of 135 volunteers, men presented higher FA values in the pathways of the cerebellum and superior longitudinal fasciculus on the left. In women, higher FA values were noted in the cerebellar pathways. These results partially coincide with our findings because men were found to have a predominance of QA of the superior longitudinal fasciculus on the left, whereas the corpus callosum showed a partial predominance of different fascicles in both study groups. Probably, these results were related to the average assessment by the authors. In various studies of the FA of the corpus callosum, the results showed the predominance of FA in men [15–17], no difference [18, 19], or partial predominance in the splenium and genu region in women [20]. These results once again demonstrate the variability of individual fascicles of the corpus callosum in men and women.

Inano et al. [21] demonstrated a difference in FA values depending on age and sex in a sample of 857 volunteers using a voxel analysis. In men, higher FA values predominated in the pathways of the splenium of the corpus callosum, corona radiata on both sides, posterior limb of the internal capsule, cerebral peduncles, external capsule, superior longitudinal fasciculus on both sides, cingulate gyrus on both sides, and middle cerebellar stalks. Moreover, women had higher FA values in the columns of the fornix. In this study, despite the use of FA and voxel analysis (FA was assessed not along the entire tract, but in a certain anatomical zone through which it passes), results similar to our study were obtained, i.e., the QA prevailed in the conducting tracts of the fornix in women and in the upper longitudinal fascicle, mainly on the left, and cingulate gyrus tracts in men. The partial predominance of FA indicators in men only in a part of the corpus callosum indicates the sex heterogeneity of this brain structure, and the voxel analysis probably did not enable full evaluation of values of this indicator along the entire conduction pathway.

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STUDY LIMITATIONS

This study has some limitations. First, the exclusion of the cerebellum from the assessment of brain conduction pathways due to the high variability of magnetic susceptibility artifacts in the posterior cranial fossa affected the reconstruction of the tracts in this area. Second, pathways were evaluated with more than 10 voxels (20 mm) long at reconstruction. This threshold was chosen to exclude several variable short tracts, which is introduced as "noise" in the results due to the need for making a large correction for multiple comparisons.

CONCLUSION

The study demonstrated sex differences in the conduction system of the white matter of the brain. The chosen approach, using modern methods of magnetic resonance imaging data reconstruction and QA as the main indicator, enabled identifying numerous differing tracts in men and women than was described in third-party studies. In addition, the difference was demonstrated not only in major anatomical tracts but also in their constituent fascicles, which in turn indicates specific sex differences in the brain structure, which cannot always be assessed using methods based on averaging of anatomical structures to relatively large units.

ADDITIONAL INFORMATION

Author contribution. *I.L. Gubskiy* — methodological support, analysis of literature, manuscript writing; *I.S. Gumin, M.A. Shorikov, M.M. Beregov* — research, manuscript writing; *L.V. Gubsky* — editing the manuscript; *V.G. Lelyuk* — methodological support, editing the manuscript. The authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

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Competing interests. The authors declare that they have no competing interests.

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