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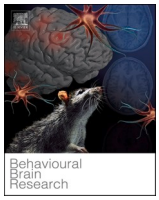

Altered thalamotemporal structural connectivity is associated with autistic traits in children with ASD

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ABSTRACT

Background: Thalamocortical functional and structural connectivity alterations may contribute to clinical phenotype of Autism Spectrum Disorder (ASD). As previous studies focused mainly on thalamofrontal connections in ASD, we comprehensively investigated the thalamic functional networks and white matter pathways projecting also to temporal, parietal, occipital lobes and their associations with core and co-occurring conditions of this population.

Methods: A total of 38 children (19 with ASD) underwent magnetic resonance imaging and behavioral assessment. Functional and structural scans were processed to analyze between-group thalamic connectivity differences and their relationships to measurements of autistic traits and language abilities.

Results: No functional differences were found between groups across 20 networks in each hemisphere. However, we showed that the diffusion properties of thalamocortical pathways projecting to the right and left temporal lobes were disrupted in children with ASD. Additionally, there was a significant association between diffusion differences of thalamotemporal tracts and severity of autistic traits.

Conclusions: Our findings on altered thalamotemporal structural but not functional connectivity contribute to the understanding of white matter organization of thalamocortical pathways in children with ASD.

1. Introduction

The abnormalities of sensory processing in Autism Spectrum Disorder (ASD) have been reported in a number of studies (e.g., [11,13,12,15]). As the central hub of sensory signals integration is the thalamus, a paired gray matter structure located above the midbrain [42], its functional and structural connectivity disruptions may contribute to sensory processing difficulties and, subsequently, to core and co-occurring conditions in ASD [13,15].

Previous studies have shown that thalamocortical structural and functional connections are altered in ASD, including thalamo-frontal [22,26,28,48], parietal [28,48], and temporal [28,48] ones. The structural characteristics are commonly measured by mean, radial, and axial diffusivity (MD, RD, AD), fractional anisotropy (FA), volume of axons, and reflect white matter integrity. Specifically, decreased FA implies such pathological processes in white matter as dysmyelination or reduced axonal myelination, lower axon density and diameter [25,47], a higher proportion of crossing fibers [20], and disorganization of fibers [2]. In the ASD population, reduced FA was found across anterior thalamic radiations (ATR; [10,50]), thalamic pathways projecting to

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anterior cingulate cortex and supplementary motor area (SMA; [28]). While FA is frequently reported to be lower across thalamocortical pathways in ASD, AD, RD, and MD have been shown to be increased in these connections. For example, all of these metrics were lower in ASD across the pathways connecting the thalamus and the right superior parietal lobule [28]. Separately, increased MD was found in the right ATR [10], in the connections projecting to the superior frontal gyri, SMAs, the left precentral gyrus, and the left temporal pole [28]. Greater AD was also demonstrated for pathways connecting the thalamus and superior frontal gyri [28]. RD was also shown to be increased for the thalamic pathway projecting to the left temporal pole and additionally across connections to precentral gyri, SMAs, the right anterior cingulate cortex, and the right superior frontal gyrus [28]. Furthermore, alterations of white matter integrity, including reduced FA and increased RD across thalamocortical pathways, were associated with more severe autistic traits, more impaired executive functions, and sensory behavior [28,48].

Functional connectivity was mostly found to be increased in ASD [28,48]. This hyperconnectivity was shown for connections of the thalamus and prefrontal cortex [48], sensorimotor cortex [21,28,4,48], temporal areas [29,48,5], and parietal cortex [21,4]. However, precisely reduced functional connectivity between the thalamus and frontal and parietal regions was related to more severe autistic symptoms, while greater connectivity between the thalamus and right fusiform gyrus was associated with better language skills and greater executive abilities [28].

Reviewing the previous studies, we highlighted that structurally thalamocortical pathways vary between the ASD and control groups. These differences are mostly connected to decreased FA and increased metrics of diffusivity. Thus, we anticipated that our results would verify these effects and add more information on other thalamocortical pathways. Functionally, we expected hyperconnectivity of thalamic networks in ASD similar to previous findings. The novelty of this study is that we used the recent parcellation approach implemented in the QIT, which allowed us to investigate 20 pathways from the thalamus in each hemisphere (https://cabeen.io/qitwiki; [9]). Also, this novel method represents a hybrid tractography algorithm for improved segmentation of complex fiber bundles combining probabilistic and deterministic tractography and is more importantly to use for projection bundles. Moreover, we aimed to compare the same parcellation for structural and functional pathways; thus, we used the structural regions of interest (ROIs) during the functional analysis. Thus, we purposed to compare thalamocortical properties between groups of children with ASD and typically developing (TD) controls and assess the relationships between behavioral measures (language skills, the severity of autistic traits) and structural and functional characteristics of the thalamus connections in children with ASD.

2. Materials and methods

2.1. Participants

Nineteen children with ASD from the Federal Resource Center for Organization of Comprehensive Support to Children with Autism Spectrum Disorders (Moscow, Russia) participated in the study (5 girls, age range 8.01–14.01 years, $M_{age} = 9.9$, $SD = 1.7$). The inclusion criterion for the group of children with ASD was diagnosis based on the International Classification of Diseases, ICD-10 [49]. Also, a licensed psychiatrist assessed 17 out of 19 children with the Autism Diagnosis Observation Schedule—Second Edition, ADOS-2 [27]. The inclusion criterion for 19 TD children (7 girls, age range 7.08–12.03 years, Mage = 9.7, SD = 1.5) was no previous history of psychiatric and neurodevelopmental conditions. The control group was recruited through social media for the current study. All participants were native Russian speakers and had no hearing or vision problems. Additionally, we obtained the Russian version of the Autism Spectrum Quotient: Children's Version, AQ [3], from parents of each child. None of the participants were excluded, as each of them met the inclusion criteria.

The HSE University Committee on Interuniversity Surveys and Ethical Assessment of Empirical Research approved the current study for TD participants' data. The approval for data of children with ASD was obtained from the local ethics committee of the Moscow State University of Psychology and Education. Conduction of the current study was in accordance with the Declaration of Helsinki. A parent of each child signed a written consent form.

2.2. Behavioral measurements

We screened non-verbal intelligence (IQ) of TD children with Raven's Colored Progressive Matrices [38,39] and non-verbal IQ of children with ASD has been screened with the Kaufman Assessment Battery for Children, K-ABC II [23], or Wechsler Intelligence Scale for Children — Third Edition, WISC-III [45]. Language performance was assessed with the Russian Child Language Assessment Battery (RuCLAB) where subtests are divided into phonological, lexical, morphosyntactic, discourse levels in both expressive and receptive domains [1].

2.3. MRI acquisition

Each child underwent structural, diffusion-weighted and functional MRI (MAGNETOM Avanto 1.5 T MRI scanner Siemens). T1-weighted isotropic scan was obtained for each child with the following parameters: repetition time (TR)= 1900 ms, echo time (TE)= 3.37 ms, 176 slices; flip angle (FA)= 15°, matrix size (MS)= 256 × 256 × 176, voxel size (VS)= 1.0 × 1.0 × 1.0 mm^3.

Single-shot echo-planar imaging sequence: b-value= 1000 s/mm^2, TR= 6800ms, TE= 97ms, 50 slices; (MS)= 96 × 96 × 50, VS= 2.5 × 2.5 × 2.5 mm^3 – was performed during diffusion-weighted imaging (DWI). Scanning for long (one non-diffusion-weighted image and 64 non-collinear diffusion directions) and short (two non-diffusion-weighted images and 12 non-collinear diffusion directions) sequences was done in anterior-posterior (AP) and posterior-anterior (PA) phase-encoding directions. Four subjects from the ASD group were scanned with only PA phase-encoding and one short sequence (AP) was acquired for them.

RS-fMRI data was obtained using the echo planar imaging sequence: TR= 3000 ms; TE= 50 ms; 35 slices; 120 volumes; FA= 90°; MS= 64 × 64 × 35; VS= 3.94 × 3.94 × 3.75 mm.

2.4. Structural data processing

The *'eddy'* function implemented in the FMRIB Software Library (FSL; [18]) was used to correct eddy-current-induced distortions and subject motion. Quantitative Imaging Toolkit software (QIT; [8]) and computational resources of HPC facilities at HSE University [24] were used to perform whole brain tractography. For each child, FA, MD, AD, RD and volume were extracted for the thalamocortical tracts. We based on the parcellation approach implemented in the QIT, thus, 20 pathways from thalamus to different cortical areas and brainstem were automatically reconstructed in each hemisphere (https://cabeen.io/qitwiki; [9]). Volume of each tract was normalized dividing by the total brain volume of each participant extracted with Brain Extraction Tool [40] from FSL (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSL). Supplementary file 1 provides information on all thalamocortical pathways terminals.

2.5. Functional data processing

RS-fMRI data was preprocessed and analyzed using the CONN toolbox Version 17.f (https://www.nitrc.org/projects/conn; [46]). Functional and anatomical data were preprocessed using a flexible pipeline [32] including realignment with correction of susceptibility distortion interactions, slice timing correction, outlier detection, direct

segmentation and MNI-space normalization, and smoothing. In addition, functional data were denoised using a standard denoising pipeline [33]. Preprocessing details are described in Supplementary file 2.

2.6. Statistical analysis

2.6.1. Structural data

Thirty-eight participants were included in the tractography data analysis (19 children in each group). Before the analysis, we ran the procedure for outlier detection for each independent variable with the following outlier removing (the outlier criterion was +-3 SD from the mean value). First, to provide between-group comparisons in each metric of each thalamocortical pathway, we fitted linear mixed-effects models, including the main effect of the sex, the age, of the tract, the main effect of the group and the interactions between the tract and the group as fixed effects, and participants as a random intercept. We applied a Bonferroni correction; thus, the results were considered significant at the $p < .01$ level (.05 / 5 - the number of tractography metrics included in the analysis). Second, to assess the relationships between the metrics of tracts and behavioral measures in children with ASD, we fitted linear models including metrics as dependent variables and three measures (non-verbal IQ, mean language score, and total AQ score).

The analysis was performed in *R* [37] with the *lme4* package [6]. T- and Wilcoxon signed-rank tests were run in *Python 3* [43] with the package *SciPy* [44]. Supplementary file 3 provides all the R and Python codes used in the analysis and visualization.

2.6.2. Functional data

Thirty-two participants were included in the functional connectivity analysis (16 children in each group). Regions of interest (ROIs) were central masses created from masks representing the center terminal of each thalamocortical tract using FMRIB's Linear Image Registration Tool [17,19]. ROI-to-ROI connectivity (RRC) matrices were estimated characterizing the functional connectivity between each pair of regions among 21 ROIs (thalamus and 20 target regions with coordinates listed in Supplementary file 1) in left and right hemispheres separately. Functional connectivity strength was represented by Fisher-transformed bivariate correlation coefficients from a general linear model (weighted-GLM; [35]), estimated separately for each pair of ROIs, characterizing the association between their BOLD signal timeseries. In order to compensate for possible transient magnetization effects at the beginning of each run, individual scans were weighted by a step function convolved with an SPM canonical hemodynamic response function and rectified. Group-level analyses were performed using a GLM [35]. For each individual connection a separate GLM was estimated, with first-level connectivity measures at this connection as dependent variables (one independent sample per subject and one measurement per task or experimental condition, if applicable), and groups or other subject-level identifiers as independent variables. Connection-level hypotheses were evaluated using multivariate parametric statistics with random-effects across subjects and sample covariance estimation across multiple measurements. Inferences were performed at the level of individual clusters (groups of similar connections). Cluster-level inferences were based on parametric statistics within- and between- each pair of networks (Functional Network Connectivity; [16,31]), with networks identified using a complete-linkage hierarchical clustering procedure [41] based on ROI-to-ROI anatomical proximity and functional similarity metrics [34]. Results were thresholded using a combination of a $p < 0.05$ connection-level threshold and a familywise corrected p-FDR < 0.05 cluster-level threshold [7].

3. Results

3.1. Behavioral data

To explore the differences in children's behavioral measures, we compared the ASD and TD groups. There was significantly higher language performance in *TD children*: $M_{ASD} = 0.75$ ($SD = 0.22$) vs. $M_{TD} = 0.95$ ($SD = 0.03$), $t(36) = -3.87$, $p < 0.001$. The severity of autistic symptoms was higher *in the ASD group*, according to AQ scores: $M_{ASD} = 84.16$ ($SD = 19.1$) vs. $M_{TD} = 49.47$ ($SD = 12.58$), $t(36) = -6.61$, $p < 0.001$. The demographic information is presented in Table 1.

3.2. Structural data

Across the thalamocortical tract projecting to the left superior temporal gyrus, we found decreased FA: $M_{ASD} = 0.40$ ($SD = 0.02$) vs. $M_{TD} = 0.42$ ($SD = 0.02$), $Est = 0.\ 23$, $SE = 0.009$, $t = 2.70$, $p = 0.007$; and increased RD: $M_{ASD} = 0.00063$ ($SD = 0.00003$) vs. $M_{TD} = 0.00061$ ($SD = 0.000024$), $Est = -0.00003$, $SE = 0.00001$, $t = -2.98$, $p = 0.003$ in the ASD group (Fig. 1).

For the tract connecting the thalamus and the right inferior temporal gyrus, we showed decreased FA : $M_{ASD} = 0.38$ ($SD = 0.02$) vs. $M_{TD} = 0.40$ ($SD = 0.02$), $Est = 0.25$, $SE = 0.009$, $t = 2.87$, $p = 0.004$; and increased MD: $M_{ASD} = 0.00091$ ($SD = 0.00005$) vs. $M_{TD} = 0.00090$ ($SD = 0.00004$), $Est = -0.00003$, $SE = 0.00001$, $t = -2.97$, $p = 0.003$ in the ASD group (Fig. 2).

For the tract connecting the thalamus and the left inferior temporal gyrus, we revealed increased RD: $M_{ASD} = 0.00069$ ($SD = 0.000045$) vs. $M_{TD} = 0.00067$ ($SD = 0.000033$), $Est = -0.00004$, $SE = 0.00001$, $t = -3.44$, $p = 0.0006$; greater AD: $M_{ASD} = 0.00128$ ($SD = 0.00007$) vs. $M_{TD} = 0.00127$ ($SD = 0.00005$), $Est = -0.00004$, $SE = 0.00001$, $t = -2.71$, $p = 0.007$; and increased MD: $M_{ASD} = 0.00088$ ($SD = 0.00005$) vs. $M_{TD} = 0.00087$ ($SD = 0.00003$), $Est = -0.00003$, $SE = 0.00001$, $t = -3.59$, $p = 0.0003$ in the ASD group (Fig. 3).

For the tract connecting the thalamus and the left middle temporal gyrus, we showed increased RD: $M_{ASD} = 0.00065$ ($SD = 0.000038$) vs. $M_{TD} = 0.00063$ ($SD = 0.000025$), $Est = -0.00003$, $SE = 0.00001$, $t = -3.10$, $p = 0.002$; and greater MD: $M_{ASD} = 0.00083$ ($SD = 0.00004$) vs. $M_{TD} = 0.00082$ ($SD = 0.00002$), $Est = -0.00003$, $SE = 0.00001$, $t = -3.22$, $p = 0.001$ in the ASD group (Fig. 4).

Other effects were not significant. The summary of the results is presented in Table 2.

3.3. Functional data

We found functional connectivity to be stronger between *left thalamus* and *left dorsolateral prefrontal cortex*, *beta* = 0.15, $t(29) = 2.99$, *p-uncorrected* = 0.006 (Fig. 5) but to be weaker between *left thalamus* and *left ventrolateral prefrontal cortices, beta* = 0.12, $t(29) = 2.19$, *p-uncorrected* = 0.04, in the ASD group (Fig. 5). The ROI-to-ROI analysis also showed weaker functional connectivity between right thalamus and right part of brainstem *beta* = -0.14, $t(29) = -2.21$, *p-uncorrected* = 0.04, in the ASD group (Fig. 5). However, this result did not remain significant after FDR-correction ($p > 0.05$).

3.4. Relationship between thalamocortical structural connectivity and clinical traits

As structural connectivity between thalamus and listed above

Table 1
Demographic characteristics.

Characteristics	ASD (N = 19)	TD (N = 19)	t	p
Age (years)	9.9 ± 1.7	9.7 ± 1.5	0.48	0.64
Mean AQ score	15.7 ± 6.5	7.8 ± 3.1	4.87	< 0.001 *
Mean language score	0.75 ± 0.22	0.95 ± 0.03	−3.87	< 0.004 *
			chi-square	p
Sex (female/male)	5/14	7/12	0.49	< 0.50

Two-sample independent t-tests were conducted to compare the mean of the demographic and behavioral data in groups of individuals with ASD and TD.

Table 2
Results of structural analysis.

Tract from thalamus to the ___ cortex	FA	RD	MD	AD
left inferior temporal	-	increased	increased	increased
left middle temporal	-	increased	increased	-
left superior temporal	decreased	increased	-	-
right inferior temporal	decreased	-	increased	-

regions differed between the groups, the relationships between volumetric/diffusion properties of these pathways and behavioral tests performance were analyzed in the ASD group. We found that decreased MD across the thalamocortical pathway projecting to the right inferior temporal gyrus: $Est = -1509000000$, $SE = 727300000$, $t = -2.074$, $p = 0.04$ and increased RD across the thalamocortical pathway projecting to the left superior temporal gyrus: $Est = 109400000$, $SE = 505900000$, $t = 2.162$, $p = 0.04$ were associated with the greater AQ scores (more severe autistic traits). Other effects were not significant.

4. Discussion

The aim of the study was to investigate the structural and functional connectivity of the thalamus between groups of children with and without ASD and assess the relationships between these differences and behavioral measures. The main finding was that thalamocortical pathways projecting to the temporal cortex differed between groups. Additionally, the analysis showed the associations between the thalamotemporal structural connectivity (increased RD and decreased MD) and more severe autistic traits in individuals with ASD.

Our main findings are decreased FA and increased AD, RD, and MD across thalamotemporal white matter pathways in children with ASD compared to TD peers. Our results on decreased FA in the thalamotemporal connections are in line with the previous reported results on reduced FA across ATR [10,50], thalamic pathways projecting to anterior cingulate cortex and SMA [28]. The FA metric is a measure of the directionality of diffusion anisotropy. As we mentioned before, reduced FA is commonly explained by axonal damages, including dysmyelination or reduced axonal myelination, lower axon density and diameter [25,47], a higher proportion of crossing fibers [20], and disorganization of fibers [2]. Thus, we may conclude that axons of tracts from the thalamus to the temporal lobe are more isotropic in children with ASD; consequently, they are damaged, and the fibers of these tracts are disorganized.

Increases of diffusivity measured by RD, AD, and MD have been shown across the thalamoparietal, thalamofrontal, and thalamotemporal pathways [10,28]. We showed that these metrics are lower for only thalamotemporal tracts. While FA is a metric reflecting more organizational information of fibers and axonal structure, different types of diffusivity provide information on diffusion itself and its directions. Thus, increased RD, AD, and MD in our study may indicate less directed water movements, the atrophy of white matter fibers, and/or alterations of axonal water content [36] across thalamotemporal tracts in children with ASD.

In contrast to Nair et al. [28], we did not find any associations between reduced FA across right frontal thalamocortical pathways or higher RD in superior frontal and superior parietal tracts and more severe autistic traits. However, we demonstrated that increased RD in the thalamic tract projecting to the left superior temporal gyrus and decreased MD in the thalamic pathway projection to the right inferior temporal gyrus were related to more severe autistic traits in the ASD group. Thus, less decreased white matter integrity [14] and more altered tissue density [30] of these pathways are linked to higher autistic symptoms.

Contrary to the studies showing hyperconnectivity between the

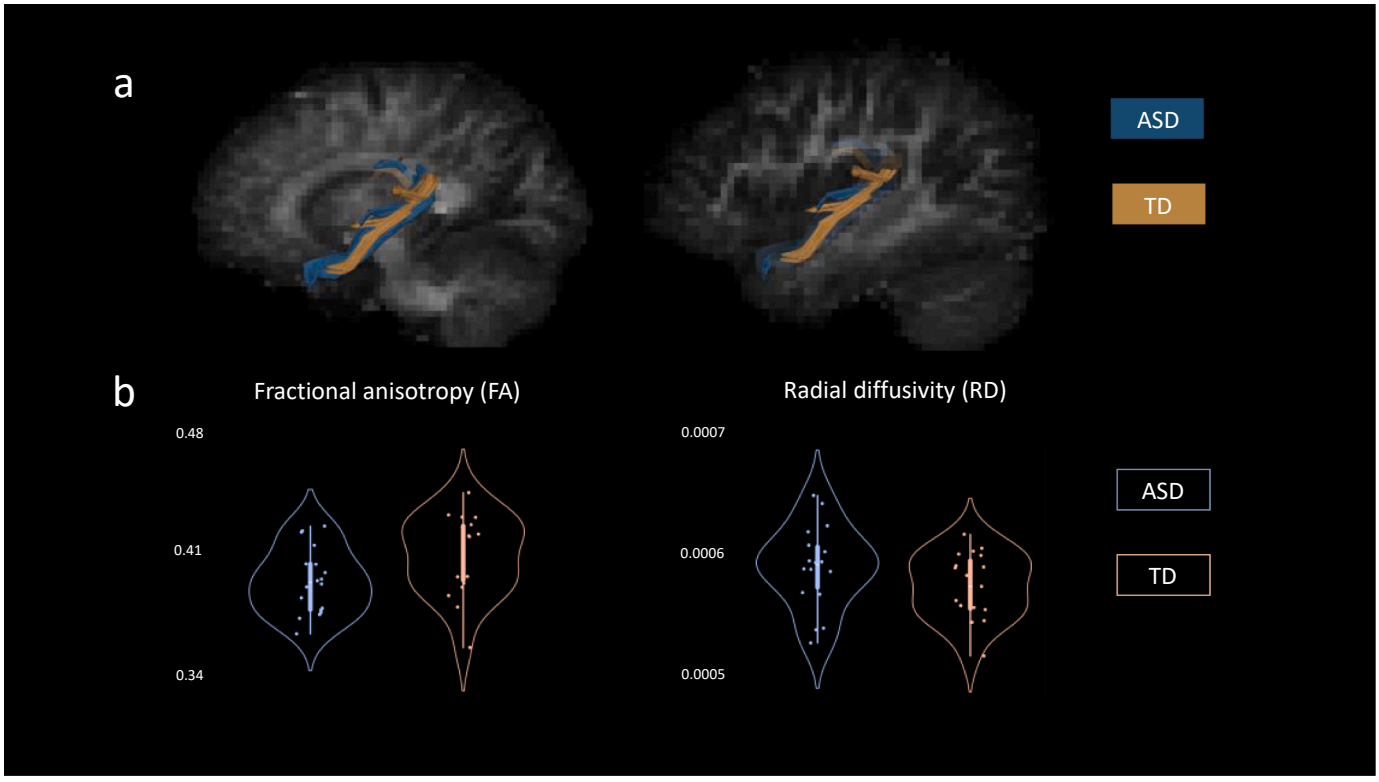

Fig. 1. Differences of the thalamocortical pathway projecting to the left superior temporal gyrus between ASD and TD a) in simplified mean bundles averaged by groups, b) in fractional anisotropy and radial diffusivity values.

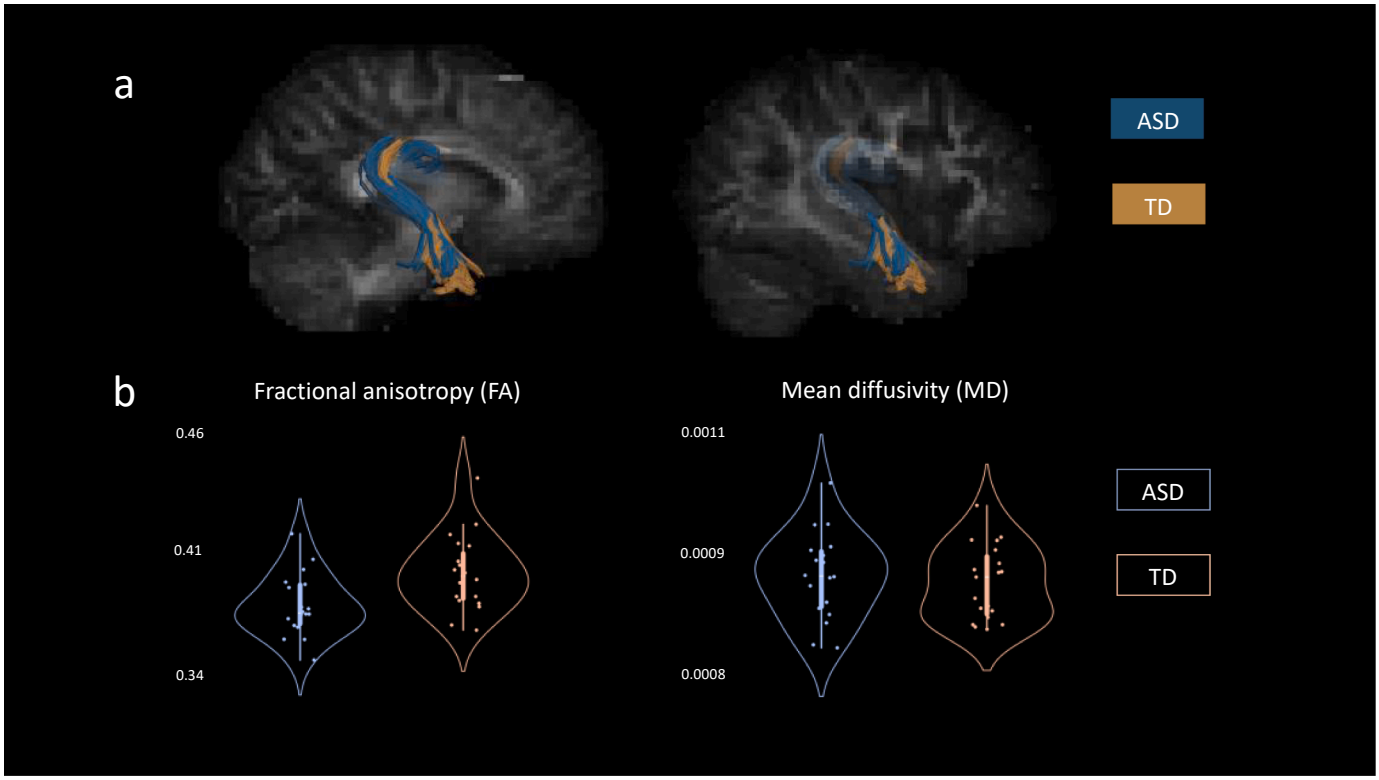

Fig. 2. Differences of the thalamocortical pathway projecting to the right inferior temporal gyrus between ASD and TD a) in simplified mean bundles averaged by groups, b) in fractional anisotropy and mean diffusivity values.

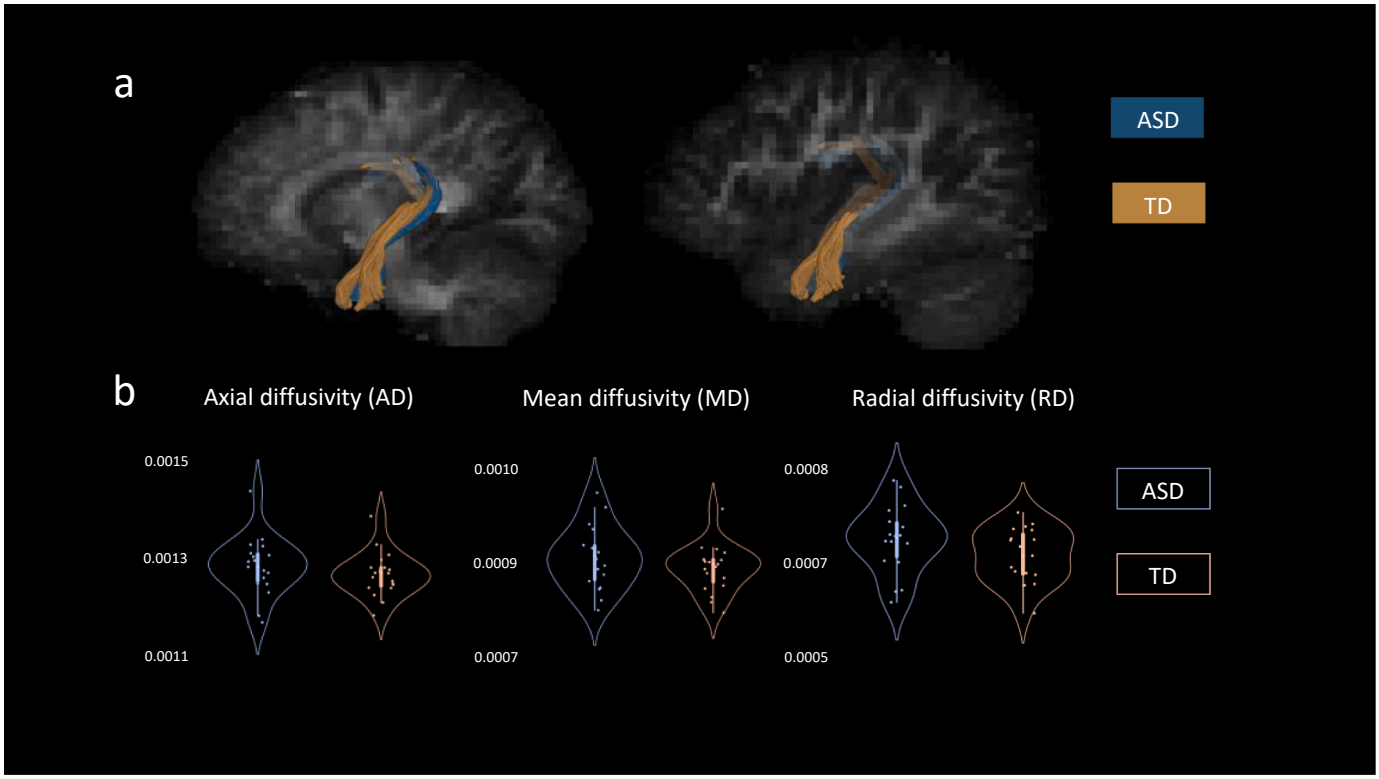

Fig. 3. Differences of the thalamocortical pathway projecting to the left inferior temporal gyrus between ASD and TD a) in simplified mean bundles averaged by groups, b) in axial, mean and radial diffusivity values.

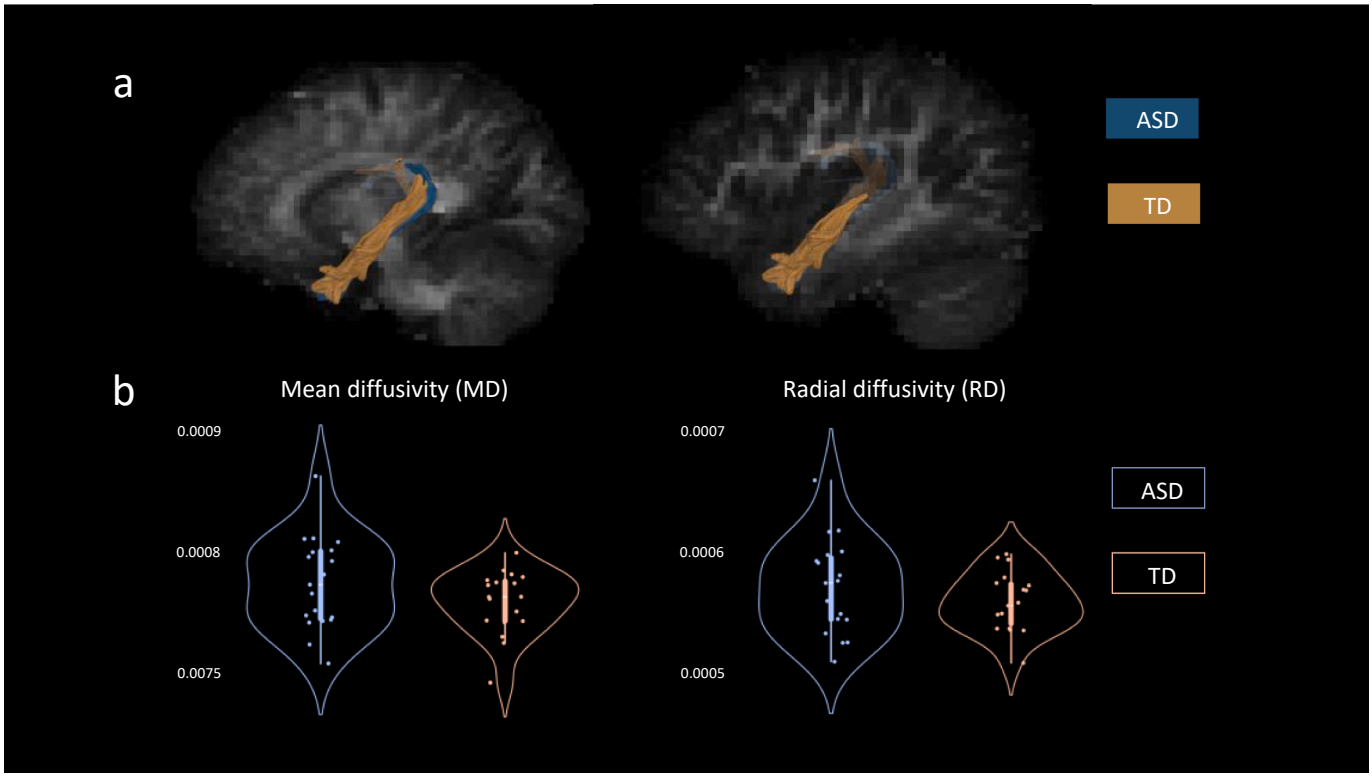

Fig. 4. Differences of the thalamocortical pathway projecting to the left middle temporal gyrus between ASD and TD a) in simplified mean bundles averaged by groups, b) in mean and radial diffusivity values.

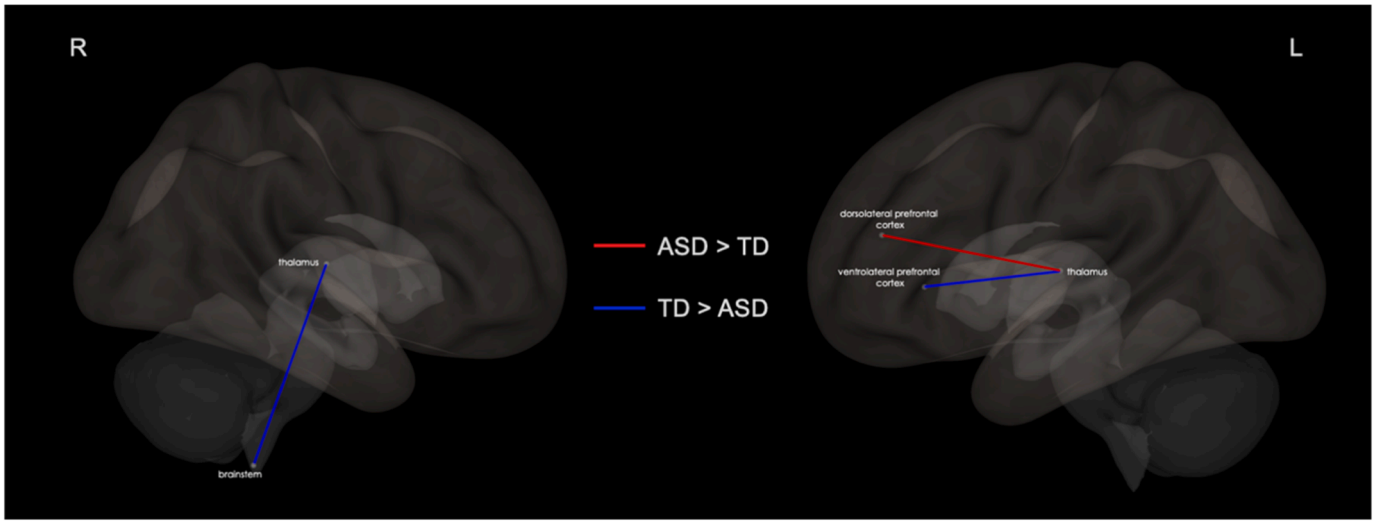

Fig. 5. Differences of the thalamofrontal and thalamostem networks between ASD and TD (before the FDR-correction).

thalamus and other brain regions, our study did not reveal these patterns [28,29,48]. One of the possible explanations is the differences of selecting target regions. We aimed to investigate the same connections structurally and functionally, thus, we created our own ROIs, while the previous studies used the atlases. One more reason for this inconsistency that our participants were younger than ones in previous research.

4.1. Limitations and future research

There are some potential limitations associated with this study. First, we measured the severity of autistic traits indirectly, using a parental questionnaire, thus, it may be more appropriate in the future to assess all behavioral characteristics using more direct tests. Second, the sample size of the current study was moderate, which could affect statistical power. Future studies may benefit from a power analysis to determine the minimum sample size. Third, dividing the thalamus into nuclei during the analysis may help to characterize its functions more specifically. Fourth, it must be noted that diffusion tensor imaging indices are not unique markers of a single tissue parameter, and any interpretation with respect to compromised myelination in ASD has to be taken with caution. Future research may focus on age-related effects of thalamocortical connections at the structural and functional levels for understanding the development and maturation trajectories and their associations with symptoms of ASD. Finally, as successful sensory

processing is nearly always required, thalamocortical connections might be related to other co-occurring traits in ASD such as impaired executive functions and/or adaptive behavior.

5. Conclusion

In the present study, we comprehensively investigated structural and functional connectivity of thalamus in children with ASD. Generally, we showed that structural but not functional thalamotemporal pathways differed between ASD and TD groups. The novel findings on altered thalamotemporal structural connectivity contribute to the understanding of white matter organization of thalamocortical pathways in children with ASD. Also, we showed that there are specific diffusion differences in the thalamocortical pathways to the temporal lobes of the autistic brain associated with more severe autistic traits in children ASD. While there are a number of studies on functional thalamic connectivity, the structural findings are limited. Our study added the information on the thalamotemporal structural connectivity postulating that the microstructure of almost all the thalamotemporal connections are altered in ASD, especially, in the left hemisphere. Moreover, these structural disruptions are implicated in the severity of autistic traits. Thus, these findings provide insights into the role of the thalamocortical connections and further our understanding of the nature of neurobiological abnormalities in ASD.

Ethical approval

The approval for this study was obtained from the HSE University Committee on Interuniversity Surveys and the Ethical Assessment of Empirical Research (for the TD group) and the local ethics committee of the Moscow State University of Psychology and Education (for the ASD group). The study was conducted in accordance with the Declaration of Helsinki.

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CRediT authorship contribution statement

Kamilla Danilina: Data curation. **Uliana Mamokhina:** Data curation. **Vardan Arutiunian:** Writing – review & editing, Supervision, Project administration, Data curation, Conceptualization. **Olga Dragoy:** Writing – review & editing, Supervision, Resources, Funding acquisition. **Darya Pereverzeva:** Data curation. **Elizaveta Davydova:** Data curation. **Svetlana Tyushkevich:** Data curation. **Alexander Sorokin:** Data curation. **Victor Karpychev:** Writing – review & editing, Methodology, Investigation, Formal analysis, Conceptualization. **Alina Minnigulova:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Consent to participate

A parent of each child signed a written consent form.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.bbr.2024.115414.

Data Availability

Data will be made available on request.

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