ARTICLE

Hypermyelination of the left auditory cortex in developmental dyslexia

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Neurology® 2018;90:e492-e497. doi:10.1212/WNL.0000000000004931

Abstract

Objective

Cortical malformations are documented postmortem in speech processing areas of the dyslexic human brain. The goal of this pilot study was to find out if such anatomic anomalies can be detected noninvasively and in vivo.

Methods

We developed a reconstruction of left perisylvian cortex profiles at a resolution of 400 μm using T1 data acquired with ultra-high-field MRI at 7T. Cortical thickness, myelinated cortical thickness, and layer-wise myelination were then compared in 6 men with developmental dyslexia and 6 healthy controls matched for age, sex, handedness, education level, and nonverbal IQ.

Results

Compared to healthy controls, dyslexic individuals showed comparable cortical thickness ($t[1,10] = 1.98$, $p = 0.311$) but significantly increased myelinated cortical thickness ratio ($t[1,10] = 3.85$, $p = 0.013$, familywise error–corrected, Cohen $d = 2.03$), resulting in an area under the receiver operator characteristic curve of 0.944 ($p = 0.010$, standard error 0.067, 95% confidence interval 0.814–1). Moreover, T1 relaxation, especially in layer IV of the left auditory cortex, was also significantly increased ($t[1,10] = 3.32$, $p = 0.043$, familywise–error corrected, Cohen $d = 1.67$).

Conclusions

Our findings provide critical insights into the neurobiological manifestation of the most common learning disorder and suggest that our approach might also shed new light on other neurodevelopmental disorders associated with cortical abnormalities.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

FWE = familywise error; **MP2RAGE** = magnetization-prepared 2 rapid acquisition gradient echoes; **ROI** = region of interest; **TA** = acquisition time; **TE** = echo time; **TR** = repetition time.

Developmental dyslexia is the most common learning disorder, occurring across cultures in every orthographic system.[1]

Specific reading and spelling deficits have been linked to various sensory and cognitive domains, but phonologic processing deficits, which are already present in infancy and persist throughout life, remain the most consistent result across writing systems.[1] In line with this, phonologic processing circuits in the left superior temporal lobe have been repeatedly found to show atypical functional responses and structural features in dyslexic samples.[1]

Genetic association studies revealed several dyslexia risk genes, with *KIAA0319*, *DYX1C1*, and *DCDC2* representing the most frequently replicated variants.[1] Knockdown of these genes in rodents disrupts the migration of nerve cell populations during intrauterine formation of the neocortex and results in gray or white matter heterotopias.[2] Gray matter heterotopias are already documented ex vivo in the perisylvian cortex of dyslexic individuals.[3]

Recently, it was proposed that dyslexia might originate from faulty neuronal migration in left auditory cortex.[4] Migration defects in layers II and III likely alter local functional interactions between layers and their global crosstalk with remote interconnected areas.[4] In addition, migration defects in layer IV are assumed to affect firing responses to auditory stimuli.[4] These microcircuitry anomalies could be related to the hallmark phonologic deficits in dyslexia.[4]

Here we reconstructed the cortical ribbon at a resolution of 400 μm isotropic to compute cortical thickness and estimate myelin concentration. Subsequently, we computed the proportional thickness of the myelinated part of the cortex in relation to its overall thickness, i.e., myelinated cortical thickness ratio. The resulting indices were then compared in a sample of dyslexic adults and healthy controls matched for age, sex, handedness, education level, and nonverbal IQ (table). We hypothesized that cortical thickness or myelinated cortical thickness ratio is significantly increased in the left superior temporal cortex of dyslexic compared to healthy controls. In addition, we predicted that increased myelination is most pronounced in layers II, III, or IV.

Methods

Participants

A pilot sample of 6 dyslexic individuals and 6 healthy controls (age range 25–32 years) were recruited in 2014 from the institute's database. All participants were native German speakers and had no history of neurologic or psychiatric conditions and normal IQ (≥85), hearing, and vision. Individuals with dyslexia received an official diagnosis during childhood by a qualified professional educator or speech therapist. Moreover, their phonologic and literacy deficits persisted into adulthood (table). Participants reported no official diagnosis of comorbid auditory processing disorder, specific language impairment, or attention-deficit/hyperactivity disorder.

Standard protocol approvals, registrations, and patient consents

All participants gave written informed consent. The study was approved by the Ethics Committee of the University of Leipzig, Germany.

MRI acquisition

Participants were scanned in 2014 on a 7T Siemens Magnetom magnetic resonance scanner with a 1-channel transmit/24-channel receive NOVA head coil.

Whole-brain T1-weighted images were acquired using a magnetization-prepared 2 rapid acquisition gradient echoes (MP2RAGE) sequence (TI1/TI2 900/2,750 ms, repetition time [TR] 5.000 ms, echo time [TE] 2.45 ms, flip angle α1/α2 5°/3°, bandwidth 250 Hz/px, GRAPPA acceleration factor 2, voxel size 700 μm isotropic, acquisition time [TA] 10:57 minutes). An adiabatic inversion pulse was implemented and dielectric pads were placed around the participants' heads to minimize sensitivity to B1 inhomogeneity.

Additional T1-weighted slabs of the temporal lobes were acquired in axial orientation (MP2RAGE: TI1/TI2 900/2,750 ms, TR 5.000 ms, TE 4.16 ms, flip angle α1/α2 5°/3°, bandwidth 240 Hz/px, voxel size 400 μm isotropic, TA 23:42 minutes).

MRI analysis

Whole-brain images were skull-stripped, rigidly aligned to Montreal Neurological Institute space, resampled to 400 μm isotropic, and segmented using a multiple object geometric deformable model. Corresponding slabs were denoised with a total variation algorithm and aligned to the whole brain images using scanner coordinates as priors. Cortical boundary surfaces were extracted using implicit surface evolution.

Volume-preserving representations of cortical depth were estimated, and myelin-sensitive cortical T1 relaxation profiles[5] were obtained from 11 equidistant points ranging from the

Table Demographic and behavioral data

	Patients with dyslexia	Healthy controls	Δ[a]
Age, y, mean ± SD	29.00 ± 2.61	27.33 ± 2.25	$t(1,10) = 1.19$, $p = 0.264$
Sex, female/male	0/6	0/6	$t(1,10) = 0.00$, $p = 1.000$
Handedness, left/right/ambidextrous	0/5/1	1/4/1	$\chi(2) = 3.11$, $p = 0.211$
Education level[b,c]	3.17 ± 0.41	2.83 ± 0.41	$\chi(2) = 2.00$, $p = 0.368$
Nonverbal IQ[c]	95.33 ± 14.10	103.33 ± 14.12	$z = 0.80$, $p = 0.485$
Verbal working memory[d] (phonologic loop)	12.00 ± 4.20	19.50 ± 4.20	$t(1,8) = 3.53$, $p = 0.008$
Text reading comprehension[e]	48.67 ± 5.61	60.67 ± 12.93	$t(1,10) = 2.09$, $p = 0.064$
Text reading speed[e]	38.83 ± 4.58	59.67 ± 10.05	$t(1,10) = 4.62$, $p < 0.001$
Spelling accuracy[f]	84.00 ± 6.03	107.00 ± 9.90	$t(1,10) = 4.86$, $p < 0.001$
Pseudoword reading accuracy[g]	12.17 ± 9.28	2.33 ± 1.51	$z = 2.51$, $p = 0.009$
Pseudoword reading speed[h]	119.52 ± 43.52	87.21 ± 29.11	$t(1,10) = 1.51$, $p = 0.166$
Phonologic awareness[i]	55.00 ± 11.87	68.25 ± 3.30	$t(1,8) = 2.59$, $p = 0.041$
Rapid automatized naming[h]	21.67 ± 2.88	16.47 ± 3.35	$t(1,10) = 2.88$, $p = 0.017$

Values are n or mean ± SD.
[a] Group difference (independent samples *t* test, Mann-Whitney *U* test, or χ^2 test).
[b] 1 = Partial high school; 2 = high school graduate; 3 = partial college; 4 = college graduate; 5 = graduate degree.
[c] Raven matrices, standard scores: mean 100, SD 15.
[d] Wechsler Adult Intelligence Scale (forward digit span), raw scores (correct repetitions).
[e] German reading speed and reading comprehension test, standard scores: mean 50, SD 10.
[f] German spelling test, standard scores: mean 100, SD 10.
[g] Raw scores (number of errors).
[h] Raw scores (seconds).
[i] German Basiskompetenzen für Lese-und Rechtschreibleistungen, raw scores (maximum 74 points).

white/gray matter boundary to the gray matter/CSF boundary. The proportional thickness of the myelinated part of the cortex in relation to its overall thickness (myelinated cortical thickness) was computed with a fuzzy classification technique combining information about radial and tangential fibers. Partial volume effects are consistent across gyri and sulci. Accordingly, local averages converge to underlying T1 values at the same cortical depth, even in strongly curved areas. Preprocessing was performed using the Medical Image Processing, Analysis, and Visualization toolbox (https://mipav.cit.nih.gov/) within the framework of the Java Image Science Toolkit (https://www.nitrc.org/projects/jist/) and the Cognitive and Brain Sciences Tools (http://www.cbs.mpg.de/institute/software/cbs-tools).

Indices were extracted from 4 regions of interest (ROIs) (core, medial belt, lateral belt, and parabelt of the left auditory cortex) defined in an independent sample of 210 healthy young adults and available in the Brain Analysis Library of Spatial Maps and Atlases (https://balsa.wustl.edu/). We transferred the annotation of each region from FreeSurfer template space into native individual space, created labels from annotations, and finally transformed each label into a volume using FreeSurfer (http://surfer.nmr.mgh.harvard.edu/). Assignment of cortical profile points to anatomic layers was based on histologic layer thickness measures of area supratemporalis simplex magnocellularis specified in the cytoarchitectonic atlas of von Economo and Koskinas.[6p672] Layer thickness was modeled as average across the entire ROI. Eleven points regularly spaced across the surface in perpendicular direction were chosen to form 10 sections sampling 10 full voxels across the average thickness of the 4 ROIs (3.98 mm).

Statistics

Continuous values were ranked to optimize normality of distribution and homogenize variance. Then independent-samples *t* tests were carried out. Mann-Whitney *U* tests were used instead whenever the data violated the normality or homogeneity assumption according to Kolmogorov-Smirnov and Shapiro-Wilk tests. Categorical dependent variables were analyzed with χ^2 tests. Two-sided *p* values are provided for demographic and behavioral data. Two-sided *p* values (familywise error [FWE]–corrected for number of regions) are reported for comparisons of cortical thickness and myelinated cortical thickness ratio. One-sided *p* values (FWE-corrected for number of layers) are reported for post hoc comparisons of layer-wise T1 values. Area under the ROC curve was computed nonparametrically. Post hoc power was calculated using G × Power (gpower.hhu.de/). All other statistical tests were run with SPSS 22.1 (IBM, Armonk, NY).

Results

Cortical thickness within the core, the medial belt, the lateral belt, and the parabelt of the left auditory cortex (figure 1A) was comparable in the dyslexic and the healthy control group (core: $t[1,10] = 1.98$, $p = 0.311$, FWE-corrected; medial belt: $t[1,10] = 0.31$, $p = 0.765$; lateral belt: $t[1,10] = 1.74$, $p = 0.311$, FWE-corrected; parabelt: $t[1,10] = 1.98$, $p = 0.311$, FWE-corrected) (figure 1B).

In contrast, myelinated cortical thickness ratio of the dyslexic individuals was significantly higher compared to healthy controls in the left auditory core region ($t[1,10] = 3.85$, $p = 0.013$, FWE-corrected, Cohen $d = 2.03$, Hedges $g = 1.88$, power 0.95). This difference was not significant in the medial belt ($t[1,10] = 1.53$, $p = 0.632$, FWE-corrected), the lateral belt ($t[1,10] = 0.79$, $p = 0.450$), and the parabelt region ($t[1,10] = 1.53$, $p = 0.632$, FWE-corrected) (figure 1C). Moreover, the effect was not found in the core region of the right hemisphere ($t[1,10] = 1.14$, $p = 0.283$). Myelinated cortical thickness ratio of the left auditory core distinguished cases from healthy controls with a sensitivity of 0.833 and a specificity of 1, resulting in an area under the receiver operator characteristic curve of 0.944 ($p = 0.010$, standard error 0.067, 95% confidence interval 0.814–1) (figure 1D).

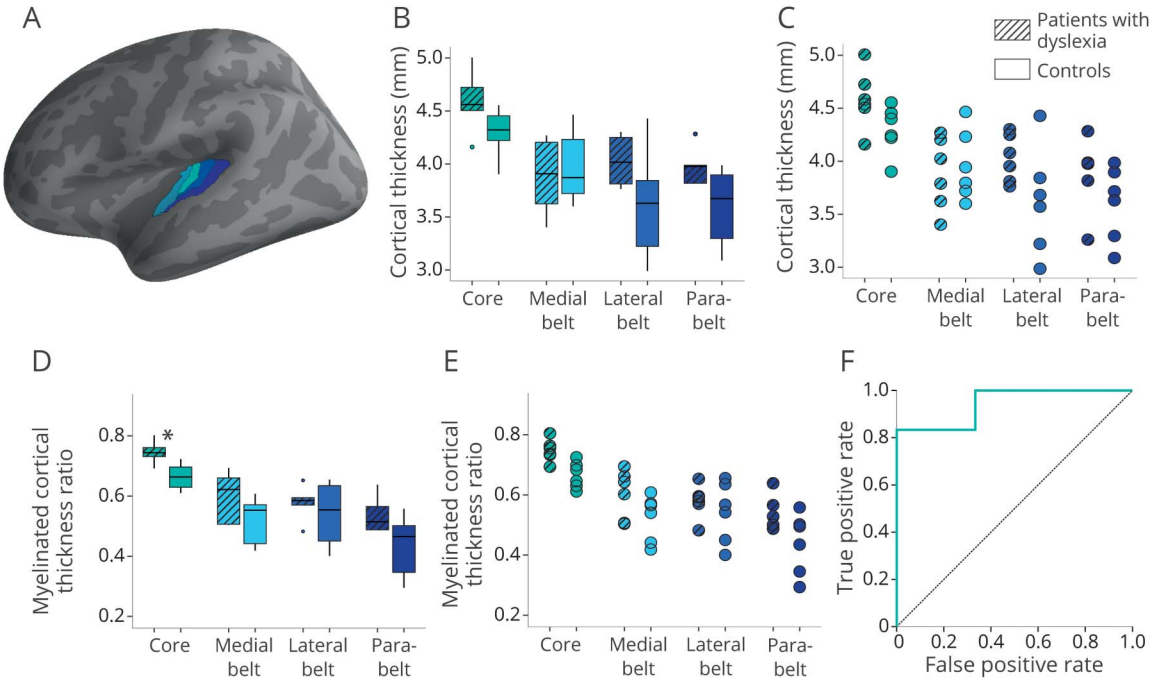
To further bolster the anatomic specificity of our results, we carried out an additional control analysis in the granular visual region (V5) and did not find a group difference ($t[1,10] = 0.63$, $p = 0.545$).

Our final step was to explore in which layers of the auditory cortex the dyslexia-specific increases in myelination originated. For this purpose, we divided the left core region into 10 sections sampling at 11 profile points. T1 value reductions in dyslexic participants vs healthy controls were significant in point 6 ($t[1,10] = 3.32$, $p = 0.043$, FWE-corrected, Cohen $d = 1.67$, Hedges $g = 1.54$, power 0.85) and point 7 ($t[1,10] = 3.32$, $p = 0.043$, FWE-corrected, Cohen $d = 1.61$, Hedges $g = 1.49$, power 0.83). Considering tissue and layer boundaries specified in the von Economo and Koskinas cortex atlas,[6] these points covered layer IV of Heschl gyrus (figure 2).

Discussion

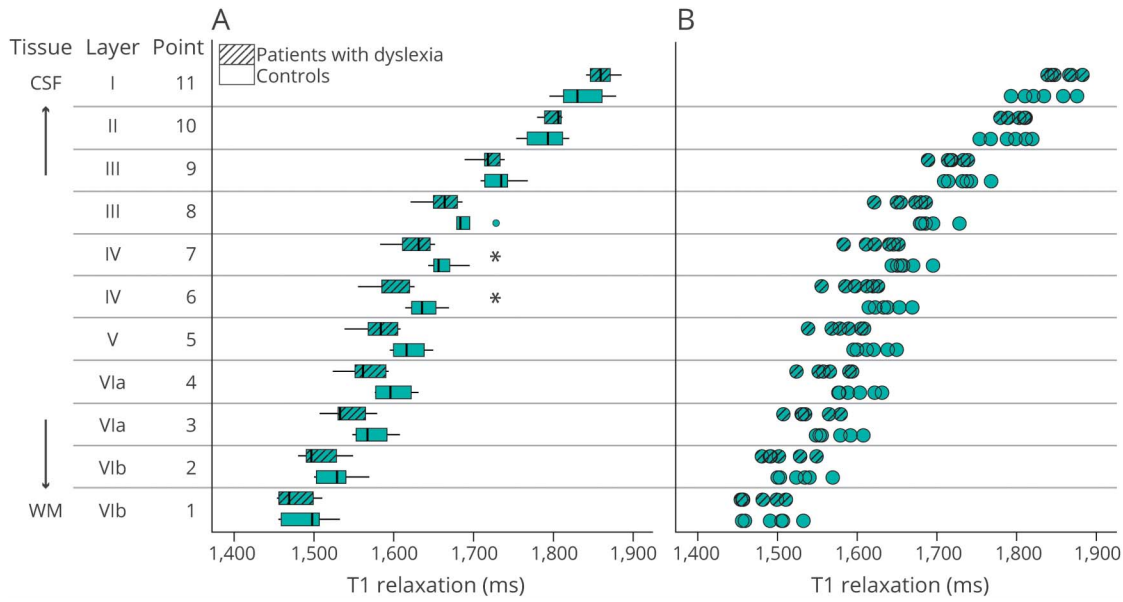
Our findings support the assumption that dyslexia is characterized by neuronal migration defects in the auditory cortex. Specifically, when neuronal populations migrate beyond their target layers, they also carry along their axons into upper layers of the cortex where they get myelinated and form white matter heterotopias reported in rodents after deactivation of

Figure 1 Dyslexia-specific intracortical hypermyelination of the left auditory core region



(A) The 4 regions of interest in the left superior temporal cortex. (B, D) Cortical thickness and myelinated cortical thickness ratio of each region plotted separately for dyslexic individuals and healthy controls. Horizontal lines within the bars represent the group median. Vertical lines at the top and the bottom of the bars depict the SD. Dots mark single cases more than 1.5 SDs away from the group mean. Asterisks indicate significant differences between groups at a familywise error–corrected threshold of $p < 0.05$. (C, E) Cortical thickness and myelinated cortical thickness ratio of each region plotted separately for dyslexic individuals and healthy controls. Dots mark individual values of each participant. (F) Receiver operating characteristic curve quantifying the accuracy of the case–control classification based on the myelinated cortical thickness ratio of the core region of the left auditory cortex. The y-axis represents the rate of correctly identified dyslexic individuals. The x-axis represents the rate of correctly identified healthy controls.

Figure 2 Layer IV origins of left auditory hypermyelination in dyslexia



The cortex was divided into 10 equally spaced sections ranging from the white matter/gray matter boundary to the gray matter/CSF boundary. Eleven profile points marking the boundaries of the sections were assigned to cortical layers based on layer thickness data available from the von Economo and Koskinas$_6$ human cytoarchitectonic atlas. T1 values in each profile point are plotted separately for dyslexic individuals and healthy controls. Note that faster T1 relaxation (i.e., lower T1 values) indicates higher myelin content. (A) Vertical lines within the bars represent the group median. Horizontal lines on each side of the bars depict the SD. Dots mark single cases more than 1.5 SD away from the group mean. Asterisks indicate significant differences between groups at a familywise error–corrected threshold of $p < 0.05$. (B) Dots mark individual values of each participant.

genes regulating layer formation.[2] Currently available data suggest that heterotopic myelin is most dense and expanded over the center of the cortex and less pronounced in superficial layers.[7] At the macroscopic level captured by MRI, this leads to an expansion of the myelinated part of the cortex and thus to an increased cortical thickness ratio in dyslexic compared to healthy control individuals.

It would be of interest to find out whether this effect is consequential or causal by applying our method to preliterate children and follow them longitudinally to assess their literacy outcome. This would also help clarify why a cortical thickness reduction in the left auditory cortex, previously described as a persistent feature of preschool children who later developed dyslexia,[8] has not been found yet in adult samples, including ours.

Myelination increase in the dyslexic group was most pronounced in layer IV, not in layers II and III, of the left core region. This has important implications for the interpretation of the effect, since it has been proposed that layers II and III generate oscillatory activity whereas layer IV regulates stimulus-driven firing during phonologic processing.[4] Interestingly and in line with our finding, delayed and inconsistent neuronal responses to speech were recently induced by knockdown of the dyslexia risk gene *KIAA0319* in the primary auditory cortex of rats, whose phoneme discrimination thresholds are nearly identical to human thresholds.[9] Impaired firing of layer IV neurons in the core region of the left auditory cortex might lead to poor phoneme distinction in dyslexia by a disrupted thalamocortical feedback mechanism. This is suggested by a previous fMRI experiment including a subset of our participants showing that blood oxygenation level–dependent activity in the medial geniculate body of the left thalamus is reduced in dyslexic individuals during phonologic processing.[10] Faulty top-down modulation of the medial geniculate body via efferent fiber connections that are densest in layer IV of the auditory cortex might hinder the auditory system from fine-tuning its responses to phonemes.[10]

Despite a small sample size, the risk of having detected false-positive effects is low given the very large conservatively estimated effect sizes and the conservative correction for multiple comparisons. It should be noted as a limitation that we cannot rule out additional intracortical anatomy differences in other regions that are beyond the resolution of our approach. Moreover, the generalizability of our results depends on their replicability in logographic readers.

Author contributions

Michael A. Skeide: study concept and design, data acquisition and analysis, data interpretation, manuscript draft, figure composition. Pierre-Louis Bazin: data analysis, critical review of manuscript for intellectual content. Robert Trampel: imaging data acquisition, critical review of manuscript for intellectual content. Andreas Schäfer: development of imaging protocols. Claudia Männel: behavioral data acquisition,

critical review of manuscript for intellectual content. Katharina von Kriegstein: data interpretation, critical review of manuscript for intellectual content. Angela D. Friederici: project supervision, data interpretation, critical review of manuscript for intellectual content.

Study funding

K.v.K. is supported by the Max Planck Society and by the European Research Council (ERC Consolidator Grant 647051 SENSOCOM).

Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Received June 28, 2017. Accepted in final form October 27, 2017.

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Cite as: *Neurology*® 2018;90:e492-e497. doi:10.1212/WNL.0000000000004931

Study question

Can abnormalities in cortical speech processing areas be noninvasively detected in patients with dyslexia?

Summary answer

MRI scans reveal expansion of the myelinated portion of the auditory cortex in the dyslexic brain.

What is known and what this article adds

Dyslexia is associated with functional and structural abnormalities in phonologic processing circuits of the left auditory cortex. This pilot study provides evidence that dyslexia-associated structural abnormalities are detectable in vivo.

Participants and setting

The participants were 6 men with developmental dyslexia and 6 healthy men matched for age, handedness, education, and nonverbal IQ. All participants were native German speakers.

Design, size, and duration

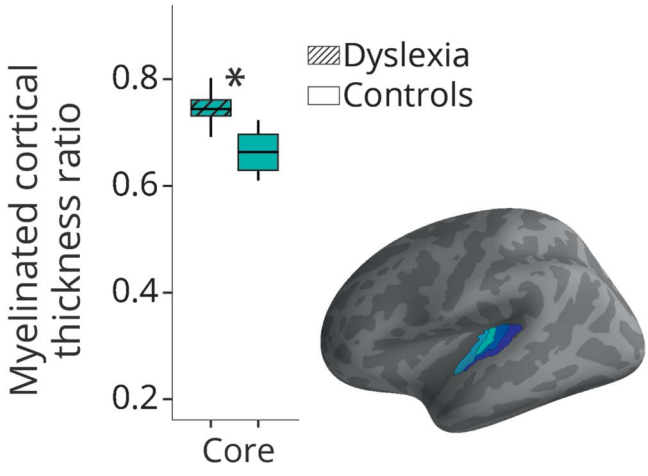
The study reconstructed each patient's left perisylvian cortex at a 400-μm resolution from T1 data acquired using ultra-high-field MRIs at 7T. The patients and healthy controls were compared for cortical property outcomes.

Primary outcomes

The primary outcomes were cortical thickness, ratios of myelinated cortical thickness to total cortical thickness, and layer-specific myelination.

Main results and the role of chance

Compared to the healthy controls, the men with dyslexia had similar cortical thicknesses ($t_{1,10}$ = 1.98; p = 0.311, family-wise error [FWE]–corrected) but greater myelinated cortical thickness ratios in the left auditory core region ($t_{1,10}$ = 3.85; p = 0.013, FWE-corrected; Cohen d = 2.03). These ratios could distinguish patients from healthy controls with an 83.3% sensitivity and a 100% specificity, which resulted in an area under the receiver operator characteristic curve of 0.944 (95% confidence interval 0.814–1; p = 0.010). The men with dyslexia also had greater T1 relaxation values, which represent layer-specific myelination, in layer IV of the left auditory cortex ($t_{1,10}$ = 3.32; p = 0.043, FWE-corrected; Cohen d = 1.67).



Bias, confounding, and other reasons for caution

The study had a small sample size, and there may be intracortical anatomic differences in regions beyond those examined in this study.

Generalizability to other populations

The patterns observed in this study may not apply to preliterate children with dyslexia. The study's results may also not be generalizable to patients who use logographic writing systems.

Study funding/potential competing interests

The authors of this study report no funding and no potentially competing interests. Go to Neurology.org/N for full disclosures.

A draft of the short-form article was written by M. Dalefield, a writer with Editage, a division of Cactus Communications. The authors of the full-length article and the journal editors edited and approved the final version.