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Lateralization of dorsal fiber tract targeting Broca's area concurs with language skills during development

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ABSTRACT

Language is bounded to the left hemisphere in the adult brain and the functional lateralization can already be observed early during development. Here we investigate whether this is paralleled by a lateralization of the white matter structural language network. We analyze the strength and microstructural properties of language-related fiber tracts connecting temporal and frontal cortices with a separation of two dorsal tracts, one targeting the posterior Broca's area (BA44) and one targeting the precentral gyrus (BA6). In a large sample of young children (3–6 years), we demonstrate that, in contrast to the BA6-targeting tract, the microstructural asymmetry of the BA44-targeting fiber tract significantly correlates locally with different aspects of development. While the asymmetry in its anterior segment reflects age, the asymmetry in its posterior segment is associated with the children's language skills. These findings demonstrate a fine-grained structure-to-function mapping in the lateralized network and go beyond our current view of language-related human brain maturation.

1. Introduction

Language development starts early in life as indicated by language-specific infant cries (Mampe et al., 2009), and the ability to distinguish different languages in the first weeks of life (Dehaene-Lambertz and Pena, 2001; Friederici et al., 2007; Nazzi et al., 1998). The adult neural language network is lateralized towards the left hemisphere (Skeide and Friederici, 2016; Toga and Thompson, 2003) and lateralization may play a crucial role during language development (Minagawa-Kawai et al., 2011). A relative leftward dominance of language-related brain regions concerning their gray matter volume (Chi et al., 1977; Witelson and Pallie, 1973) and their function (Dehaene-Lambertz et al., 2002, 2006) is evident already in infants, and becomes more pronounced with age (Amunts et al., 2003; Qi et al., 2019; Szaflarski et al., 2006; Everts et al., 2009; Olulade et al., 2020; Perani et al., 2011). Hence, the organization of language-related cortical brain regions appears to be asymmetric already in early development and becomes more lateralized with emerging language abilities.

Information transfer between the brain regions within the language network is enabled by distinct white matter pathways connecting language-relevant regions located in the prefrontal and temporal cortices (Catani et al., 2005; Friederici and Gierhan, 2013; Skeide and Friederici, 2016). Such white matter fiber bundles composed of millions of axons surrounded by myelin allowing the fast transmission of electrical impulses between brain regions (Wake et al., 2011). For the adult brain, previous literature describes two main language-related information streams, one running dorsally, and the other ventrally relative to the Sylvian fissure (Hickok and Poeppel, 2007; Friederici, 2011; Fridriksson et al., 2016; Forkel et al., 2022), and are considered to play distinct functional roles in language processing (Brauer et al., 2013; Friederici, 2009; Saur et al., 2008).

The ventral pathway is taken to support semantic processes and comprehension (Saur et al., 2008; Turken and Dronkers, 2011; Catani and Bambini, 2014). This pathway can be subdivided into two fiber bundles one connecting the most anterior inferior frontal cortex and the anterior temporal cortex, known as the uncinate fascicle, functionally related to local combinatorics of words and one connecting the frontal cortex to the temporal cortex, known as the inferior-fronto-occipital fascicle (IFOF), functionally related to sentence level semantic processes (Friederici and Gierhan, 2013). The dorsal pathway consists of two white matter fiber bundles targeting different region in the frontal cortex (Catani et al., 2005; Gierhan, 2013; Perani et al., 2011). Together

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these two bundles are named arcuate fascicle and their functions are often not separated. One fiber bundle targets the posterior Broca's area (BA44) and the other one targets BA6, and they appear to serve different functions. The BA44 targeting fiber tract was found to support the processing of complex syntactic structures (Friederici et al., 2006) and the processing of complex sentences as indicated by clinical (Wilson et al., 2011) as well as developmental studies (Skeide et al., 2016). The BA6 targeting fiber tract was discussed to support auditory-to-motor mapping (Hickok and Poeppel, 2004; Friederici and Gierhan, 2013), and subserve sentence repetition (Saur et al., 2008). While the BA6-targeting tract is already myelinated at birth (Perani et al., 2011), the BA44-targeting tract matures much later. This difference in the fiber tracts' developmental trajectory may suggest a functional difference between the two dorsal fiber tracts with only the BA44 targeting fiber tract supporting sentence comprehension (Skeide et al., 2016) and the BA6 targeting fiber tract supporting auditory-to-motor mapping already present in the prelinguistic infant.

Thus far it is also unclear how the leftward asymmetry of the structural language network emerges during childhood - particularly the asymmetry of the two dorsal tracts. This, however, is crucial to understand the biological preconditions underlying the functional and structural lateralization observed in adults (Thiebaut de Schotten et al., 2011; Eichert et al., 2019) and during development (Skeide and Friederici, 2016; Enge et al., 2020). While some studies observe left-hemispheric lateralization already in infancy (Lebel and Beaulieu, 2009; Reynolds et al., 2019; Dubois et al., 2009; O'Muircheartaigh et al., 2013), others report symmetrical arrangement of the dorsal tract up to 3 years of age (Salvan et al., 2017; Song et al., 2015). Furthermore, from previous research, it remains unclear whether and how the asymmetry of the dorsal language tracts relates to language development. While leftward asymmetry has been positively associated with phonological processing (Lebel and Beaulieu, 2009) and reading skills (Qiu et al., 2011), others found the opposite pattern (Catani et al., 2007; Yeatman et al., 2011), or no correlation between asymmetry and language function (Reynolds et al., 2019). Thus, although asymmetry is considered a hallmark of the adult human language network (Eichert et al., 2019), its relation to language development remains debated.

Three factors may have contributed to the observed inconsistencies in the previous findings.

First, in the studies reviewed above, the dorsal language tract has often collectively been referred to as the *arcuate fascicle*, not considering that this pathway comprises at least two coherent fiber bundles with distinct structural terminations in the frontal cortex (BA6 and BA44). The blending of these functionally distinct pathways for language might have contributed considerable variability in previous findings.

Second, an important limitation of previous studies lies in a monolithic view of tract structure. As such, microstructural parameters were typically summarized over the entire length of the fascicle leading to a macrostructural view. However, novel analysis strategies suggest that microstructural properties vary considerably across white matter tracts (Yeatman et al., 2011, 2012). Thus, tract-wise summaries of microstructural parameters may have led to inconsistent findings across previous research.

Third, studies relating dorsal tract asymmetry with language development have only rarely investigated the early preschool period. This developmental period, however, marks a critical take-off in many language abilities, particularly in the ability to process complex sentences (Akhtar, 1999; Fox and Grodzinsky, 1998; Guasti, 2017), and may thus be an ideal window to investigate the relationship between dorsal tract asymmetry and language skills.

In the current study we draw on a large sample of preschool children from 3 to 6 years of age to investigate the emergence of dorsal tract asymmetry and its association with the development of language abilities – tested by a sentence comprehension test, and moreover, its association with age in order to delineate these two factors. In contrast to previous studies, we delineate two dorsal fiber bundles, one terminating in BA44 and the other in BA6, to account for their distinct functional roles and developmental trajectories in early childhood (Perani et al., 2011; Brauer et al., 2013). In addition to a macrostructural tract-wise analysis, we leverage a localized approach to study the lateralization of microstructural properties along the length of the tracts (Yeatman et al., 2011, 2012) to allow a more fine-grained investigation of the lateralization of the language-related white matter fiber bundles and their association to language development in young children.

2. Materials and methods

2.1. Subjects

An initial sample of 278 children between 3 and 7 years of age was considered for the present study. The data were collected across several projects by our group (Skeide et al., 2016; Cafiero et al., 2019; Fengler et al., 2016; Kuhl et al., 2020). All subjects were native German speakers, with no history of medical, psychiatric, or neurological disorders. Written informed consent was obtained from the legal guardian or parent of the children in accordance with approval from the Ethics Committee at the Faculty of Medicine of the University of Leipzig.

Before preprocessing the data, we excluded 90 children due to one of the following reasons: 1) no or incomplete dMRI data ($n = 18$); 2) no or incomplete anatomical data ($n = 33$); 3) left-handedness ($n = 29$, according to the Edinburgh Handedness Inventory) (Oldfield, 1971) or 4) a verified later diagnosis of dyslexia ($n = 10$). The remaining 188 datasets, including children within an age range of 3.04–7.02 years (87 female, median = 5.26 years, SD = 0.8 years), underwent preprocessing and quality checking (see *dMRI Data Analysis*). We excluded 32 datasets because of bad image quality (e.g., due to large head motion in the dMRI data, as described in the section Quality Control). Thus, we performed analyses in a sample of 156 children, with an age range of 3.04–6.93 years (72 females, median = 5.29 years, SD = 0.77 years). These children (except for one child) all attended the Kindergarten and were not yet at school. The distribution of age and the inclusion procedures are illustrated in Supplementary Material (Figure S3, S4).

2.2. Behavioral data

2.2.1. Assessment of language development

A subsample of 90 children, with an age range of 4.08–6.93 years (43 females, median = 5.33 years, SD = 0.58 years), additionally underwent a standardized language test (German: “Test zum Satzverstehen von Kindern, TSVK”, English: “Sentence Comprehension Test for Children”) (Siegmüller et al., 2010). The age distribution of the subsample is illustrated in the Supplementary Material (see Figure S4).

The TSVK assesses general sentence comprehension abilities using a picture-matching task, in which children are auditorily presented with a sentence and three pictures of which only matched the sentence. In a total of 36 items, the child is asked to choose the picture that best matches the auditorily presented sentence. The two distractor pictures differed either in the syntactically marked Actor-Patient-Relation or semantically in the content words describing the respective pictures (see examples in Supplementary Material). Further, the items vary in sentence complexity, manipulated by word order, tense, mode, clause number, pronoun type, and verb type. To preserve individual developmental differences in the language scores, we summed the correct responses and z-transformed raw values rather than using normalized T-scores. We excluded three subjects from the analyses that were identified as outliers in the language performance data, resulting in a dataset of 87 children, with an age range of 4.08–6.93 years (42 females, median = 5.35 years, SD = 0.58 years). Language development scores were significantly related to age ($r = 0.38$, $p < .001$; see Supplementary Material S5).

2.2.2. Assessment of non-verbal cognitive abilities

Non-verbal IQ was assessed either by using the Kaufman Assessment Battery for Children (Kaufman, 1983) or the Wechsler Preschool and Primary Scale of Intelligence (Petermann, 2011). As in previous studies (Qi et al., 2021), the non-verbal IQ scores from these tests were viewed as equivalent due to standardization and high intercorrelation. All children (N = 156) had a non-verbal IQ within the normal range, with a mean of 107.76 (SD = 10.76).

2.3. MRI data acquisition

Neuroimaging data were acquired on a 3 Tesla Trio MRI system (Siemens Healthineers, Erlangen, Germany), using a 12-channel head coil (Siemens Healthineers, Erlangen, Germany) and Syngo Software Version B17. Diffusion MRI (dMRI) data were acquired using optimized monopolar Stejskal–Tanner Echo Planar Imaging (EPI) sequence (Morelli et al., 2010) (TR = 8000 ms; TE = 83 ms; 100 ×100 image matrix; FoV = 186 ×186 mm^2; 66 axial slices (no gap); spatial resolution: 1.86 ×1.86 ×1.9 mm^3), Partial Fourier = 0.75, GRAPPA = 2. 60 isotropically distributed diffusion-encoding gradient directions with a b-value of 1000 s/mm^2 were scanned along an anterior-to-posterior phase encoding direction. Seven interspersed b = 0 s/mm^2 images were additionally acquired as anatomical reference for image correction after each block of 10 diffusion-weighted images. A second set of images was acquired along a posterior-to-anterior phase encoding direction, including one b = 0 s/mm^2 image and one b = 1000 s/mm^2 diffusion-weighted volume. High-resolution 3D T1-weighted MRI images were acquired using the MP2RAGE sequence (Marques et al., 2010) (TR = 5000 ms, TE = 2.82 ms, TI_1 = 700 ms, TI_2 = 2500 ms, α1 = 4°, α2 = 5°, matrix size = 144 ×168×192, voxel size = 1.3 ×1.3 ×1.3 mm^3). Before MRI scanning, children were acquainted with the scanning procedure by performing a mock scan to playfully familiarize them with the experimental environment and procedures.

2.4. MRI data analysis

2.4.1. Preprocessing

The preprocessing of the dMRI data entailed the following steps (Fan et al., 2022) in the described order: (i) Debiasing: The non-Gaussian noise distribution of MRI may result in skewed model fits or loss of contrast for low signal-to-noise (SNR) data, such as dMRI (Eichner et al., 2015). Hence, the dMRI data were debiased using the underlying noise distribution (St-Jean et al., 2020). The relevant parameters were determined locally from the dMRI data (St-Jean et al., 2020). (ii) Denoising: We used MP-PCA denoising with default parameters to increase the SNR of the dMRI data. (iii) Unringing: Gibbs ringing artifacts were removed using the sub-voxel shift algorithm. (iv) Distortion Correction: Eddy current and off-resonance-induced image distortions were corrected in an integrated approach, which accounts for motion-induced changes in susceptibility fields. (v) Drift Correction: We corrected for signal drifts using a second-order polynomial fit to the non-diffusion-weighted data (Vos et al., 2017).

The preprocessing of the structural MP2RAGE data entailed the following steps in the described order. (i) Background noise removal of the MP2RAGE UNI image, a combination of the two inversion time images (O'Brien et al., 2014). (ii) Reorientation to standard (MNI) orientation, registration to standard space (linear and non-linear), and brain extraction using the fsl_anat pipeline (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/fsl_anat). (iii) ACPC alignment of the denoised and preprocessed UNI image using the Automatic Registration Toolbox (https://www.nitrc.org/projects/art). The diffusion data were then aligned to the structural UNI image using the dtiInit preprocessing pipeline in the VISTASOFT package (https://github.com/vistalab/vistasoft).

2.4.2. Tractography and automated fiber quantification

We used the Automated Fiber Quantification (AFQ) software (Yeatman et al., 2012; Kruper et al., 2021; Bain et al., 2019) to generate global and local macrostructural information on the microstructural diffusion properties of a predefined set of white matter tracts. The python-based pyAFQ software implements several processing steps to produce robust axonal models and results in tract profiles from which diffusion metrics were derived:

i. A whole-brain tractography map was generated using Constrained Spherical Deconvolution as a local model (Tournier et al., 2004). Whole-brain probabilistic tractography (Yeatman et al., 2011) was started in randomly selected initialization points with a fixed number of streamlines per voxel within the whole-brain mask (min length = 10 mm, max length = 1000 mm, max angle = 30, step-size = 0.5).
ii. The resulting whole-brain tractogram was then segmented into individual fiber bundles. This was done by classifying whether an individual fiber runs through specific predefined waypoint regions of interest that define the anatomical trajectory of the fascicle (Wakana et al., 2007). These waypoints were defined in MNI space and then registered to the individual's native space via non-linear transformation. In addition, fiber bundles were filtered based on their endpoints relative to regions defined in the AAL atlas (Tzourio-Mazoyer et al., 2002).
iii. Fiber tract refinement was implemented by overlaying each candidate fiber to fiber tract probability maps and discarding fibers with a low probability of belonging to the predefined fiber bundle (Hua et al., 2008). This ensures that each streamline in the resulting fiber bundle runs through the predefined waypoints, is projected to the predefined endpoints, and conforms with the central trajectory of the tract. By default, pyAFQ provides such segmentation procedures for 18 standard tracts.
iv. The resulting fiber bundles were cleaned of fibers that significantly differed from the mean position of the tract bundle. The cleaned tracts were visually checked by a trained rater, to ensure that fiber bundles were clearly segmented and robustly identified across subjects. To promote the robustness of local parameter estimation, the fibers were then clipped to the central fragment between the two defining ROIs.
v. The core of the fiber bundle was computed by resampling each fiber into 100 equidistant nodes and calculating the mean location of each node. Local tissue diffusion properties (i.e., FA, MD) along the tract were then evaluated at each node by using a weighted mean approach. The weights were determined based on the Mahalanobis distance of each fiber's node to the core node. This resulted in tract profiles depicting diffusion properties along the length of the fiber bundles.

The applied AFQ combination of (iii) tract probability maps, (iv) tract cleaning and clipping, and (v) distance weighting aimed at extracting diffusion measures predominantly from white matter voxels close to the core tract. Our analyses were focused on white matter tracts understood to be important for language processing. This included the dorsal tracts targeting Broca's area (BA44) and the premotor cortex (BA6), respectively, along with the ventral language tract corresponding to the IFOF. In addition, we used the corticospinal tract as a control tract. To delineate the two dorsal tracts, we modified the default segmentation procedures of the *arcuate fascicle*, implemented in pyAFQ. In particular, we adapted the endpoints of the tract definition, yielding BA44 or BA6, respectively, relying on definitions in the Harvard-Oxford cortical atlas (Makris et al., 2006). For the dorsal tract targeting BA6, we additionally used an exclusion mask in BA44 and an exclusion mask to prevent streamlines from bending into the corticospinal tract. This procedure resulted in clearly segmented dorsal tracts targeting BA44 and BA6, respectively (see Supplementary Material S2 for details). For the segmentation of the IFOF and corticospinal tract, we relied on the default segmentation procedures implemented in pyAFQ. The tracking recipes are summarized in Figure S5 of the Supplementary Material.

2.4.3. *Deriving lateralization indices in macrostructure and microstructure*

For macrostructural characterization of asymmetry of each pathway, a lateralization index, $\mathrm{LI}_{\mathrm{macro}}$, was computed using the (cleaned) streamline count, *c*, of each brain hemisphere, generated by the above-described procedures:

$$\mathrm{LI}_{\mathrm{macro}} = \frac{c_{\mathrm{Left}} - c_{\mathrm{Right}}}{c_{\mathrm{Left}} + c_{\mathrm{Right}}}$$

To characterize local asymmetry on the microstructural level, a localized lateralization index, $\mathrm{LI}_{\mathrm{micro}}(\mathrm{node})$ was calculated for each microstructural parameter, $p_{\mathrm{Left/Right}}(\mathrm{node})$ (i.e., FA, MD), projected on the respective, localized at each node of a fiber pathway:

$$\mathrm{LI}_{\mathrm{micro}}(\mathrm{node}) = \frac{p_{\mathrm{Left}}(\mathrm{node}) - p_{\mathrm{Right}}(\mathrm{node})}{p_{\mathrm{Left}}(\mathrm{node}) + p_{\mathrm{Right}}(\mathrm{node})}$$

This approach resulted in a lateralization profile for each tract (see Fig. 1c).

The LI approach helps to mitigate biases in tractography results (e.g., from algorithm choice, brain size, signal-to-noise ratio, etc.), as both hemispheres are equally influenced by such global factors. Therefore, LI is a robust metric to study macrostructural and microstructural effects of brain lateralization.

2.4.4. *Quality control*

To maintain high-quality fiber reconstructions, we leveraged a cascade of quality control criteria along the entire processing pipeline. (i) The quality of the dataset was assessed using the eddy QC tools (Bastiani et al., 2019). This tool provides an objective quality control for dMRI data based on quantitative data-quality parameters. Subjects with a heavy movement larger than two standard deviations of the eddy movement parameter across the group were flagged as outliers and excluded from further analysis. (ii) Gradient directions were checked on the FA image for correct reconstruction of prominent anatomical structures, such as the optic radiation, corpus callosum, and cortico-spinal tract. (iii) Brain extraction was checked on the diffusion and structural data. (iv) To ensure correct tracking results we additionally inspected each individual reconstruction of the tracts of interest to ensure a robust identification of tracts across subjects. The criteria to check for correct tracking are summarized in Figure S6 of the Supplementary Material.

2.4.5. *Statistical analysis*

Partial correlation analyses were implemented to relate microstructural and macrostructural lateralization indices of each tract with the age and language performance of the children. In the analysis relating lateralization to age, we included gender, absolute head motion in the scanner, and handedness as covariates of no interest to control for their potential influences.

In the analysis relating lateralization to language performance, we additionally included age as a covariate to control for general maturational effects. Further, we controlled for non-verbal IQ to make sure that the identified effects were solely related to language and not to cognitive

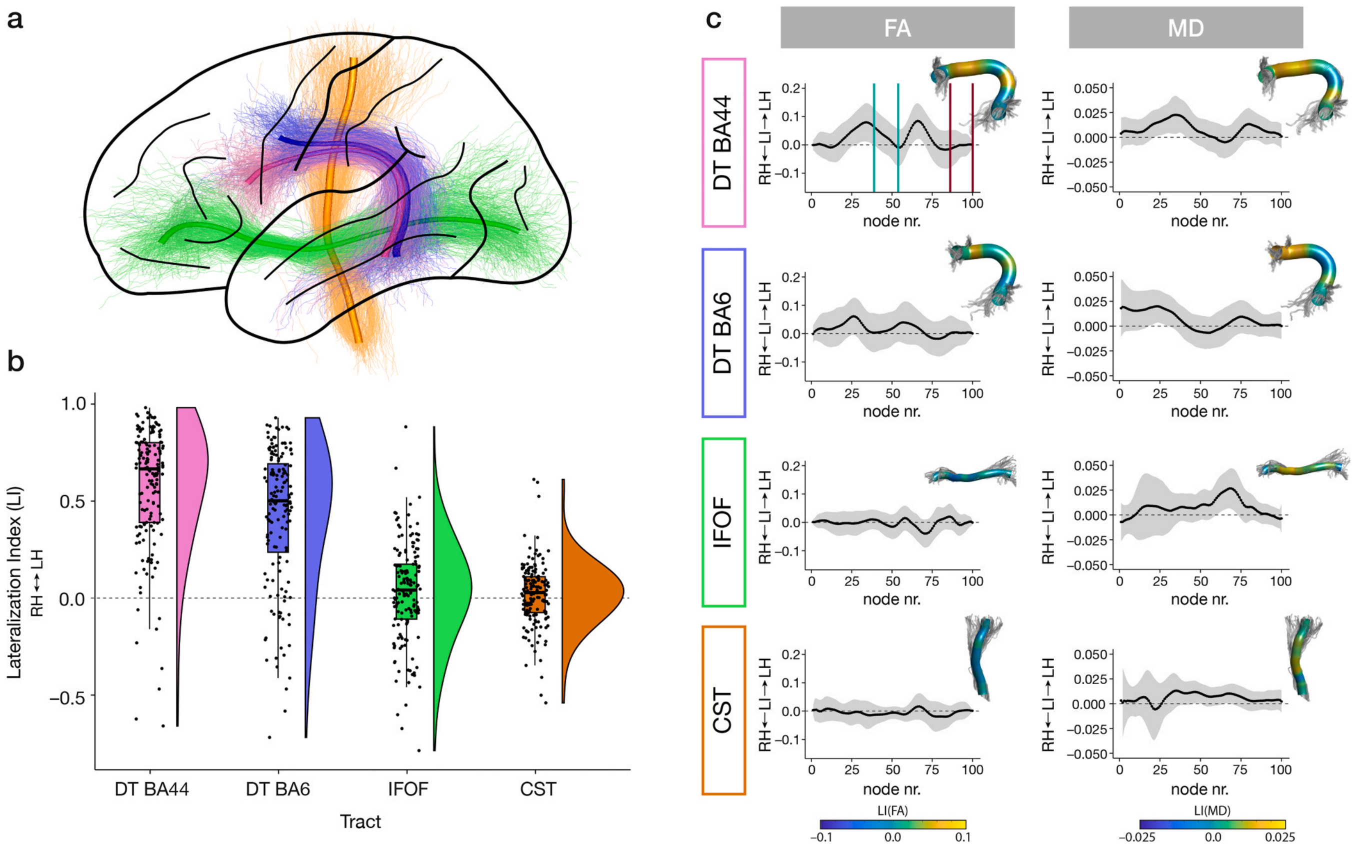

Fig. 1. **: (a)** Tractography reconstructions for the dorsal tract targeting BA44 (DT BA44; orange), the dorsal tract targeting BA6 (DT BA6; blue), the ventral tract (IFO; green), and the corticospinal tract (CST; magenta) using the automated fiber quantification software [43]. For each tract, the figure displays a random sample of 500 streamlines (thin lines) across all subjects alongside the respective centroid tract (bold lines), used for the subsequent analyses. **(b)** Summary of tract-wise macrostructural asymmetry. A positive lateralization index (LI) indicates leftward asymmetry. **(c)** Localized microstructural lateralization profiles for fractional anisotropy (FA) and mean diffusivity (MD). A positive lateralization index (LI) indicates leftward asymmetry. The gray-filled areas indicate the respective local standard deviations. For visualization, microstructural lateralization indices are additionally plotted on a representative tract. Vertical lines in cyan and red indicate the regions of DT BA44 segments that correlate with age and language, respectively.

functioning per se. We also performed supplementary analyses checking for the effects of gender and handedness on lateralization (see Supplementary Material S8 & S9).

The local microstructural analyses, which were performed pointwise along the fiber tracts, resulted in an increased number of univariate statistics on the same dataset. To appropriately adjust for multiple comparisons, we used a nonparametric permutation-based correction (Nichols and Holmes, 2002) to compute the I-corrected cluster size. Significance was set at $p = 0.05$ for all analyses, as well as for cluster-based permutation corrections.

3. Results

3.1. *Structural asymmetry of the language network*

To investigate the structural asymmetry of the language network, we reconstructed the dorsal and ventral language pathways, together with a control tract (i.e., the corticospinal tract; see Fig. 1a). We calculated lateralization indices on the macrostructural level, as in previous studies, using the number of reconstructed streamlines. Further, we applied a localized, node-based approach to receive more fine-grained information on microstructural asymmetry along the length of the fiber bundles (Yeatman et al., 2012).

3.2. *Macrostructural asymmetry*

In Fig. 1b, we summarize the macrostructural lateralization of the tracts in focus. On the macrostructural level, we find that the dorsal tract targeting BA44 is left-lateralized in 94.87% of children, while the one targeting BA6 is left-lateralized in 83.33% of children. On average, the dorsal tract targeting BA44 showed a lateralization index of LI = 0.56 +- 0.32, whereas the dorsal BA6 tract indicated a lateralization index of LI = 0.41 +- 0.36. This difference in lateralization of the dorsal tracts is significant (paired t-test, $T(155) = 6.09$, $p < .001$). In contrast, the ventral tract and the corticospinal tract did not show clear indications for macrostructural lateralization (see Fig. 1b).

3.3. *Localized microstructural asymmetry*

In Fig. 1c, we show localized lateralization profiles of the microstructural parameters Fractional Anisotropy (FA) and Mean Diffusivity (MD) for the here studied tracts. We find that FA and MD asymmetry of the dorsal tract targeting BA44 is not uniformly distributed along the length of the bundle, but rather shows two peaks in the anterior-horizontal and posterior-vertical portions of the tract. In those outlined segments, leftward microstructural lateralization was most pronounced. Similar patterns can be observed for FA and MD profiles along the dorsal tract targeting BA6, showing two outlined segments in similar locations, but those were not as clearly pronounced as for the bundle targeting BA44. We calculated the mean lateralization of FA across tracts and performed a paired t-test comparing lateralization of the dorsal tract targeting BA44 and BA6. The results show that FA lateralization is significantly greater in the dorsal tract targeting BA44 ($t = 4.96$, $p < 0.001$). For the ventral pathway, we did not find a clear asymmetry of FA along the tract. For MD we observed one left-lateralized peak in the frontal segment of the IFOF. The corticospinal tract did not show clear indications of lateralization in the microstructure.

3.4. *Development of structural asymmetry in the preschool age*

We investigated the developmental trajectory of macro and microstructural asymmetry of the language network in the preschool period. To this end, we related the age of the children to their macrostructural lateralization (i.e., in the number of streamlines) and local microstructural lateralization profiles. This was done using partial correlation analyses, in which we controlled for gender and handedness of the children, as well as for absolute subject motion in the scanner.

On the global macrostructural level, no significant (partial) correlation was observed between age and asymmetry of (i) the dorsal tract targeting BA44 ($r_p = -0.11$, $p = 0.163$), (ii) the dorsal tract targeting BA6 ($r_p = -0.02$, $p = 0.853$), (iii) the ventral tract ($r_p = -0.11$, $p = 0.165$), or (iv) the corticospinal tract ($r_p = -0.11$, $p = 0.165$).

On the localized microstructural level, we find that FA asymmetry in the anterior-horizontal part of the dorsal tract targeting BA44 is significantly related to age ($r_p = 0.22$; $p = 0.003$; see Fig. 2). For the other tracts, no significant correlation between microstructural diffusion parameters and age was observed.

3.5. *Relationship between structural asymmetry and language development*

To investigate the relationship between asymmetry and language development, we performed partial correlation analyses, relating macrostructural asymmetry and microstructural lateralization profiles to the language development of the children, controlling for non-verbal IQ, age, gender, absolute subject motion, and handedness.

On the macrostructural level, no significant (partial) correlation was observed between language development and asymmetry of (i) the dorsal tract targeting BA44 ($r_p = 0.04$, $p = 0.699$), (ii) the dorsal tract targeting BA6 ($r_p = 0.01$, $p = 0.989$), (iii) the ventral tract ($r_p = 0.04$, $p = 0.693$), or (iv) the corticospinal tract ($r_p = -0.11$, $p = 0.299$).

On the localized microstructural level, however, we find that FA asymmetry in the posterior-vertical part of the dorsal tract targeting BA44 is significantly related to language performance ($r_p = 0.28$; $p = 0.004$; see Fig. 3). For the other tracts, no significant correlation between microstructural diffusion parameters and language performance was observed.

4. Discussion

The dominance of the left hemisphere is a defining feature of the adult language network which has been consistently observed for function (Dehaene-Lambertz et al., 2002, 2006) and structure (Chi et al., 1977; Witelson and Pallie, 1973) of language-related cortical brain regions, as well as the dorsal white matter pathways connecting these regions (Eichert et al., 2019; Lebel and Beaulieu, 2009; Reynolds et al., 2019). The lateralization of language-related brain regions, developing throughout early childhood has been suggested to be a fundamental mechanism underlying language capabilities (Szaflarski et al., 2006; Minagawa-Kawai et al., 2011; Groen et al., 2012; Qi et al., 2019). However, to date, it remained unclear when the asymmetry of language-relevant white matter pathways emerges and how this relates to language development.

In the current study, we investigate the macrostructure and the microstructure of the language-related white matter pathways. We present evidence from a large sample of preschool children between 3 and 6 years ($N = 156$) showing that localized microstructural asymmetry in the dorsal language network structurally matures during early childhood and how it functionally relates to language performance. We will discuss these issues in turn.

4.1. *Lateralization of the dorsal pathways*

In the adult human brain, several structural language pathways have been identified either running dorsally or ventrally to connect the prefrontal with temporal language areas. Macrostructural analyses consistently report leftward lateralization of the dorsal pathway in the adult brain when defining it as one collective fiber bundle (Thiebaut de Schotten et al., 2011; Eichert et al., 2019). However, the dorsal language pathway has been shown to consist of two fiber bundles with distinct structural terminations - one targeting BA44 and one targeting BA6.

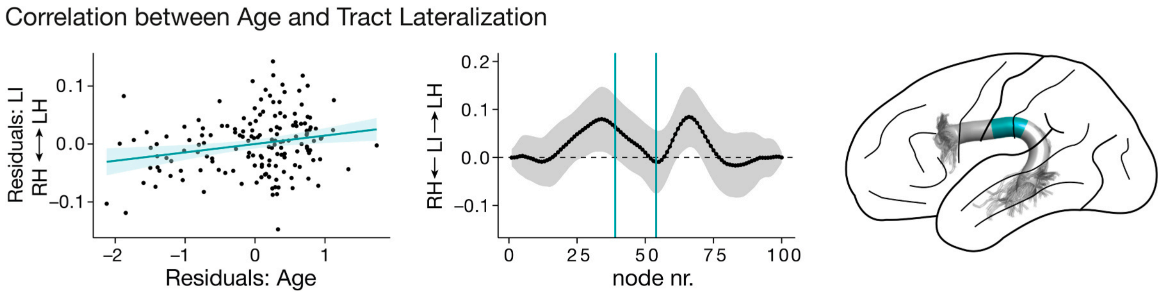

Fig. 2. **:** Significant partial correlation of age with microstructural lateralization in fractional anisotropy (FA) in the anterior-horizontal part of the dorsal tract targeting BA44 (cyan segment; $rp = 0.22$; $p = 0.003$). This effect is independent of gender and handedness of the children, as well as of absolute subject motion in the scanner. The scatter plot shows the correlation between the two sets of residuals from age and lateralization indices while holding gender, handedness, and motion in the scanner constant. The cyan-filled area in the scatter plot indicates the 0.95 confidence interval.

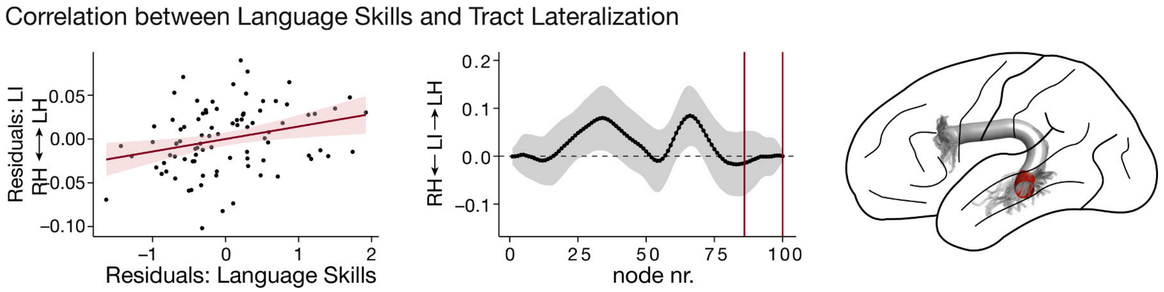

Fig. 3. **:** Significant partial correlation of language skills with microstructural lateralization in fractional anisotropy (FA) in the posterior-vertical part of the dorsal tract targeting BA44 (red segment; $r_p = 0.28$; $p = 0.004$). This effect is independent of gender, handedness, non-verbal IQ, age, and absolute motion in the scanner. The scatter plot shows the correlation between the two sets of residuals from language skills scores and lateralization indices while holding gender, handedness, and motion in the scanner constant. The red-filled area in the scatter plot indicates the 0.95 confidence interval.

These two bundles account for different functional roles in language processing (Friederici and Gierhan, 2013; Brauer et al., 2013; Friederici, 2009; Glasser and Rilling, 2008). A structural subdivision of the dorsal pathway has previously been identified into a direct and an indirect segment, targeting BA44 and BA6, respectively (Catani et al., 2005). The dorsal tract connecting the premotor cortex (BA6) with temporal cortices, functionally required for auditory-to-motor feedback learning during infancy, is already in place at birth (Perani et al., 2011; Brauer et al., 2013). The ventral pathway (IFOF) is also already well developed and strongly myelinated at birth (Perani et al., 2011). In contrast, the second dorsal tract connecting the posterior part of Broca's area (BA44) with the temporal cortex emerges late during childhood and was found to correlate with the development of complex language features, such as syntax (Brauer et al., 2013; Skeide et al., 2016).

For preschool children, our macrostructural analysis provides evidence that these two distinct dorsal fiber bundles in the language network differ in their lateralization already during early development. This contrasts with the ventral language tract, which did not show consistent lateralization. The two dorsal fiber bundles are both clearly left-lateralized, although the BA44 tract is significantly more lateralized than the BA6 tract. This observed pattern of lateralization to the left is generally in line with previous macrostructural analyses which take the dorsal language pathway as a single coherent tract (Eichert et al., 2019). However, the significant difference in the lateralization between the two dorsal language tracts targeting BA44 and BA6 found here, raises the question of whether the analyses in previous studies were sufficiently detailed to identify neurobehavioral correlates for the asymmetry of the arcuate fascicle, or its subparts.

4.2. *Microstructural asymmetry and correlates*

The microstructural analysis of diffusion properties (i.e., FA and MD) along the pathways (Yeatman et al., 2012; Kruper et al., 2021) which we employed here provides a more detailed picture of the white matter asymmetry, indicating that the microstructural asymmetry is not uniformly distributed along the two dorsal tracts. Rather the microstructural analysis shows a leftward asymmetry for segments along the tracts, located in anterior-horizontal and posterior segments (see Fig. 1). The observed leftward asymmetry in these segments was found to be more pronounced in the tract targeting BA44 than in the tract targeting BA6. These microstructural results are generally consistent with a recent structural study that focused on the lateralization profile of the *arcuate fasciculus* as one tract in the adult brain (Bain et al., 2019), but the observed microstructural local asymmetry for the different segments is correlated with different developmental aspects, namely age on the one hand, and language skills on the other.

A significant correlation was found between FA and age in the anterior-horizontal portion of the dorsal pathway targeting BA44, indicative of an age-related leftward increase in tract strength. This local difference in the lateralization strength of the fiber tract raises the question of its functional significance. From previous studies we know that frontal brain regions mature later than temporal regions, (a) in their gray matter volume (Gilmore et al., 2007; Knickmeyer et al., 2008), (b) in their gray matter involvement in language processing between the age of 3 and 4 years (Klein et al., 2022) as well as (c) in their functional activation during language processing between 3 and 9 years (Skeide et al., 2014). This increase in the involvement of the gray matter may lead to the here observed age-related increase of tract strength in the anterior-horizontal segment of the dorsal BA44 tract, as previous work has shown that the age-related expansion of the gray matter co-occurs with an increase in the white matter terminations in the cortex (Cafiero et al., 2019). Given the age-related changes in the frontal cortex, its gray matter and its involvement in language function, the observed age-related changes in the anterior-horizontal segment of the BA44 tract suggest a relation between the functional and structural development in the frontal cortex.

The functional microstructural analysis further revealed that the asymmetry of the dorsal fiber bundle targeting BA44 in Broca's area, and not the one targeting BA6 in the premotor cortex, is positively related to the performance of more complex language functions, i.e., sentence comprehension, at preschool age. This association was restricted to a small segment of the BA44 targeting tract, located in its most posterior part, in the temporal lobe. This result is intriguing as such dorsal temporal projections have previously been associated with emergence of the human ability to process language across the primate lineage (Rilling et al., 2008; Rilling, 2014; Balezeau et al., 2020).

The finding that the posterior-temporal segment correlates with language performance may find its explanation in the observation that the temporal which is part of the adult language network (Friederici, 2011; Pallier et al., 2011) partly changes its tasks during development (Skeide et al., 2014). The involvement of the temporal cortex in sentence comprehension changes across development qualitatively and also spatially. In 3–4-year olds the mid-superior temporal gyrus activates as an interaction of semantic and syntactic processes, whereas in 6–7-year olds semantic and syntactic processes recruit different parts of the superior temporal gyrus and sulcus, with semantics recruiting the mid temporal gyrus and syntax recruiting the posterior temporal gyrus and sulcus in addition to an interaction effect. No main effect of syntax is found in these children between 3 and 7 years. Only by the age of 9–11 years a main effect of syntax is observed in the inferior frontal gyrus. Thus there is a change in the function of different subregions the temporal cortex during language development from a local involvement of the middle part of the posterior temporal gyrus to separated parts distributed along the temporal gyrus for semantic and syntactic processes (Skeide et al., 2014). At the age of 9–11 years the main effect of syntax in the inferior frontal gyrus covers BA44 and BA45, and it is only in adults that the syntax effect is confined to BA44. This is in line with a study investigating children at the age of 10–15 years reporting a gradual selectivity of BA44 for syntactic processes (Nuñes et al., 2011). The involvement of the posterior temporal cortex in processing syntactically complex sentences in addition to semantic processes in the adult language system has recently been agreed on in the scientific community (Matchin and Hickok, 2020; Grodzinsky et al., 2021; Zaccarella et al., 2017). In adults the function of the temporal cortex is taken to reflect the integration of semantic and syntactic information, available in the mid temporal cortex and the posterior superior temporal cortex respectively. The functional change in the use of the temporal cortex during development goes together with a maturation of the fiber tract connecting the temporal cortex to BA44 which in turn correlates with an interesting performance as evidenced in macrostructural analysis of the fiber tract (Skeide et al., 2016) in processing syntactically more complex sentences. Here in our microstructural analysis we find a correlation of the posterior-vertical segment of the BA44 targeting tract and language comprehension possibly reflecting its increased involvement during semantic-syntactic integration processes.

At the microstructural level, this relationship between language performance and localized FA lateralization may be due to stronger fiber coherence (Kruper et al., 2021), resulting from a larger functional involvement of the left temporal lobe during sentence processing. A better functional integration of semantic and syntactic processes would be achieved by an increase of white matter fiber connections of the BA44 targeting tract in the cortical surface of semantic and syntax-related areas of the temporal lobe (Cafiero et al., 2019). This hypothesis is supported by consistently elevated FA values in the left hemisphere (Supplementary Material Figure S1), indicative of increased fiber coherence. Also, the cortical projections of the reconstructed dorsal tracts suggest that a larger part of the temporal lobe is connected in the left hemisphere (Supplementary Material Figure S2). Post-hoc analyses indicate that the observed behavioral correlation in the posterior AF is not solely driven by the left AF. Instead, it seems to reflect a mixed effect, where the left AF shows positive correlation with language and the right AF shows negative correlation with the AF (Supplementary Material Figure S10). Our microstructural results suggest that the development of dorsal tract asymmetry is determined by the maturation of small segments within the fiber bundle targeting BA44, but not for the fiber bundle targeting BA6. Note that in contrast to these localized microstructural effects, we did not identify significant changes in macrostructural asymmetry with age. These macrostructural findings are in line with previous studies suggesting that macrostructural asymmetry of the language-related network may be established already at an earlier developmental stage, possibly even in infancy (Lebel and Beaulieu, 2009; Reynolds et al., 2019). Here, we extend these initial results and show in our study that the lateralization of the structural language network continues to develop at the microstructural level.

In summary, the present microstructural findings indicate a lateralization of the dorsal fiber tract targeting BA44 in Broca's area, but not the one targeting the premotor cortex nor the ventrally located fiber tract or the control tract. The observed lateralization does relate to age and language performance, though in different segments of the fiber tract. Our microstructural results show that similar to functional and gray matter structural asymmetry on the regional level (Szaflarski et al., 2006; Minagawa-Kawai et al., 2011; Groen et al., 2012; Qi et al., 2019), regional white matter asymmetry does contribute to successful language development in the preschool period. The present data do not allow us to provide explanations with respect to the genetic or cellular underpinnings of the observed laterality effects. As we set out to investigate the development of the lateralization of the language network our analysis is restricted to this aspect.

5. Conclusion

In summary, the present microstructural findings demonstrate a lateralization of the dorsal fiber tract targeting BA44 in Broca's area, but not of the one targeting the premotor cortex nor the ventrally located fiber tract or the control tract. The observed lateralization relates to age and language performance, though in different segments of the fiber tract. Our more fine-grained analysis of white matter asymmetry in the language network revealed novel neurobehavioral correlates in early childhood, allows a better understanding of the inconsistencies observed in previous studies by providing a more precise view of the complex neural underpinning of language development.

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CRediT authorship contribution statement

Cornelius Eichner: Writing – original draft, Writing – review & editing, Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Visualization. **Angela Friederici:** Conceptualization, Funding acquisition, Methodology, Resources, Supervision, Writing – original draft, Writing – review & editing. **Cheslie C. Klein:** Data curation, Investigation, Methodology, Visualization, Writing – review & editing. **Philipp Berger:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing.

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.

Data availability

Data will be made available on request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.pneurobio.2024.102602.

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