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The relationship between white matter architecture and language lateralisation in the healthy brain

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Abstract

Interhemispheric anatomical differences have long been thought to be related to language lateralisation. Previous studies have explored whether asymmetries in the diffusion characteristics of white matter language tracts are consistent with language lateralisation. These studies, typically with smaller cohorts, yielded mixed results. This study investigated whether connectomic analysis of quantitative anisotropy (QA) and shape features of white matter tracts across the whole brain are associated with language lateralisation. We analysed 1040 healthy individuals (562 females) from the Human Connectome Project database. Hemispheric language dominance for each participant was quantified using a laterality quotient (LQ) derived from fMRI activation in regions of interest (ROIs) associated with a language comprehension task compared against a math task. A linear regression model was used to examine the relationship between structural asymmetry and functional lateralisation. Connectometry revealed a significant negative correlation between LQs and QA of corpus callosum tracts, indicating that higher QA in these regions is associated with bilateral and right-hemisphere language representation in frontal and temporal regions, respectively. Left language laterality in temporal lobe was significantly associated with longer right inferior fronto-occipital fasciculus (IFOF) and forceps minor tracts. These results suggest that diffusion measures of microstructural architecture as well as geometrical features of reconstructed white matter tracts play a role in language lateralisation. People with increased dependence on right or both frontal hemispheres for language processing may have more developed

commissural fibres, which may support more efficient interhemispheric communication.

Significance statement: The left cerebral hemisphere is dominant for language functions in most people. In some healthy people, language functions are lateralised to the right hemisphere or distributed across both hemispheres. The anatomy underlying patterns of hemispheric language dominance are not well established. Emerging evidence suggests that white matter connectivity and architecture is an important feature of cortical functional organisation. In this work, we report that people who have language functions distributed across both hemispheres have greater inter-hemispheric connectivity compared to lateralised people. Our findings provide further insights into the anatomical basis of language function and may have wider clinical implications.

Introduction

It has long been hypothesised that grey matter asymmetries of regions that support language function may be associated with functional lateralisation of language in the human brain (Güntürkün et al., 2020). Associations between cortical asymmetries and hemispheric language dominance (HLD) have been noted in some studies of Wada-tested patients with epilepsy (Dorsaint-Pierre et al., 2006; Foundas et al., 1996, 2002; Keller et al., 2018) and healthy controls who underwent structural and functional MRI (Josse et al., 2009; Keller et al., 2011). However, other studies have reported no association between HLD and structural hemispheric asymmetry in classical language cortical areas (Chiarello et al. 2013; Greve et al. 2013). Attention has recently shifted towards the importance of white matter as the basis of lateralised cortical function. Some studies have reported that leftward language lateralisation is associated with a greater volume of the arcuate fasciculus (Propper et al., 2010) and the number of tracts in the corpus callosum (Timocin et al., 2020). More recently, HLD has been investigated using microstructural DTI properties, such as fractional anisotropy (FA), in patient cohorts (Tantillo et al., 2016; Barba et al.,

2020). Some studies have reported relationships between language lateralisation and diffusion characteristics or the size of the corpus callosum (Tantillo et al., 2016), while others did not (Barba et al., 2020). There are limited functional MRI (fMRI)-DTI studies on language lateralisation in healthy individuals. Tractography studies have reported associations between fMRI-determined left HLD and FA of the left arcuate fasciculus (James et al., 2015; Perlaki et al., 2013; Powell et al., 2006; Silva & Citterio, 2017) and corpus callosum (Häberling et al., 2011). However, other studies have not reported relationships between the side or extent of HLD and conventional diffusion-based tract characteristics (Karpychev et al., 2022; Vernooij et al., 2007), as well as more sophisticated diffusion MRI measures, such as fibre density cross-section (Verhelst et al., 2021). Inconsistencies between studies may be due to methodological differences, including differences in tractography approaches, study designs, patient characteristics, and sample sizes.

In the present study, we adopted two complementary approaches that potentially overcome some of the methodological shortcomings of previous tractography studies. First, we employed a connectometry approach based on an local analysis of diffusion properties, which uses permutation testing to identify group differences along white matter tracts. This whole-brain approach employs correlational tractography to identify specific subcomponents of white matter tracts that exhibit anisotropy correlated with a predefined variable of interest with superior sensitivity and specificity compared to traditional voxel-based analyses (Yeh et al., 2016). Connectometry has recently been used to uncover structural disparities between bilingual and non-bilingual individuals (Rahmani et al., 2017) and to identify structural pathways linked to enhanced language capabilities in individuals with aphasia (Hula et al., 2020; Dresang et al., 2021) and preterm-born children (Barnes-Davis et al., 2020, 2022). Second, we employed shape analysis to investigate the geometrical characteristics of white matter tract bundles that comprise the integral components of language networks. This approach captures fundamental shape characteristics, such as volume and surface area, and encompasses advanced morphological properties including white matter bundle curl, elongation, length, span, and diameter (Yeh, 2020). Previous studies have already demonstrated, through the utilization of virtual dissections (Catani et al., 2007) and shape analysis employing tractography algorithms (Yeh et al., 2020), that the leftward morphometric

asymmetries of language-associated white matter tracts exist in people without known hemispheric language dominance (HLD). Whether white matter interhemispheric asymmetries change in people with atypical HLD remains unclear.

The first objective of the present study was to conduct diffusion connectometry analysis in a large cohort of healthy individuals who underwent language fMRI to determine whether microstructural properties of white matter tracts are related to HLD. The second objective was to explore whether interhemispheric shape asymmetries of white matter tracts are related to language lateralisation in the same individuals.

Methods

Study data and participants

All data were acquired from the Human Connectome Project (HCP) (http://www.humanconnectome.org/) open-access data initiative offering high-quality anatomical and functional MRI of the human brain. We used the HCP Young Adults (HCP-YA 1200 Subjects) data release as it contains a large sample of healthy adults for whom both language task fMRI and diffusion MRI sequences were acquired. The dataset comprised 1200 healthy adults, aged 22-35 years. Each participant underwent an identical imaging protocol acquired on the same MRI scanner. Individuals with neuropsychiatric or neurologic disorders, diabetes, high blood pressure, premature birth, and severe symptoms associated with substance use were excluded from data collection (Van Essen et al., 2013). The present study focused on language fMRI and diffusion MRI data only. Individuals were only selected for inclusion if they had fMRI data available for the language story task (see below) and had corresponding 3T diffusion MRI data. This resulted in a sample size of 1040 participants (562 females), with a mean age of 28.74 (SD = 3.69) years. According to the Edinburgh Handedness Inventory (Oldfield, 1971), 962 (92%) participants preferred their right hand, scoring at least 10 on a scale of -100 (left) to 100 (right). Eighty-five participants preferred left, scoring below -10, and two were ambidextrous, scoring zero.

Data acquisition

HCP data were acquired on a Siemens 3T Skyra system, with 32-channel (SC72) head coil. Task fMRI data were collected using gradient-echo echo-planar imaging (EPI) with an isotropic resolution of 2.0 mm (TR = 720ms, TE = 33.1ms, matrix = 104x90, 72 slices, flip angle = 52°, BW = 2290 Hz/Px, FOV = 208 x 180 mm, 72 slices, multiband accelerator factor = 8) (Marcus et al., 2013). The HCP dMRI data were acquired using three shells (b=1000, 2000 and 3000 s/mm2) with 90 diffusion gradient directions and five b_0 volumes with RL phase encoding direction (TE = 89.5ms, TR = 5520ms, flip angles = 78/160°, isotropic voxel size = 1.25 mm3, multiband factor = 3) (Sotiropoulos et al., 2013).

Language paradigm

The language comprehension task used in Human Connectome Project was designed by Binder and colleagues (2011). The task consists of two 3.8-minute runs. Each run has four blocks of story tasks alternating with four blocks of math tasks. The story and math tasks are matched in terms of length, word and phoneme rate, speaking style, and prosodic features. The story blocks present subjects with 5-9 auditory sentences, followed by questions about the content of the story. The math task requires participants to perform arithmetic operations followed by equals and two choices. Since arithmetic tasks do not engage temporal lobe activity (Baldo & Dronkers, 2007), we decided to use a STORY-MATH contrast, as it effectively isolates regions responsible for language comprehension without “masking” temporal lobe activity. Additionally, temporal lobe is involved in high-level processes of normal consciousness (Spitsyna et al., 2006), thus we avoided passive tasks as a baseline to reduce the risk of masking activities in this region (which is essential for language comprehension). This contrast allowed us to cancel out the regions that are jointly activated in both tasks (such as low-level auditory and phonological input), isolating the regions involved in narrative processing including semantic and non-speech related aspects of language, theory of mind, and inference processing.

fMRI preprocessing and analysis

The preprocessed task fMRI data were retrieved from HCP database (https://db.humanconnectome.org). The HCP pre-processing included *fMRIVolume* and *fMRISurface* pipelines, which were primarily built using tools from FSL (Jenkinson et al., 2012; http://www.fmrib.ox.ac.uk/fsl), Freesurfer (Fischl, 2012) and the HCP Workbench (Marcus et al., 2013). Details of the pre-processing steps have been described previously (Glasser et al., 2013). The goal of the first *fMRIVolume* pipeline was to generate 4D whole-brain timeseries. This was accomplished by (1) removing spatial distortions by gradient non-linearity distortion correction, (2) realigning volumes using rigid-body motion correction using a single-band reference image as the target, and (3) estimating (using FSL toolbox “topup”) and correcting field map-based EPI distortions. The resulting EPI data was (4) registered to T1-weighted scan, then (5) non-linearly (FNIRT) into Montreal Neurological Institute (MNI) space, and (6) blood-oxygen-level−dependent (BOLD) signal intensity was normalized by the average. This process resulted in individual subjects being mapped with a notable degree of left-right symmetry (Elam et al, 2021), which aligns with laterality research recommendations (Vingerhoets et al., 2023).

The goal of *fMRISurface* pipeline was to transform the resulting 4D timeseries to Connectivity Informatics Technology Initiative (CIFTI) grayordinate space, encompassing cortical, subcortical, and cerebellar grey matter collectively (Pham et al, 2022). This was accomplished by mapping fMRI data within cortical grey matter ribbon onto the native cortical surface, registering it into CIFTI grayordinate space (surface representation with 32,492 vertices on each hemisphere), and mapping the set of subcortical grey matter voxels from each subcortical parcel in each individual to a standard set of voxels in each atlas parcel, resulting in 2mm average surface vertex and subcortical volume voxel spacing. Finally, grayordinate space data was smoothed using Gaussian kernel.

We used a fully processed task-based STORY-MATH fMRI activation Contrast Of Parameter Estimates (COPE) map, which was generated by FSL FEAT and is readily available on https://db.humanconnectome.org as part of the “S1200 Subjects” dataset. Considering the spatial heterogeneity of the individual brain scans, the MSM-All (Multimodal Surface Matching) registered dataset was used, which uses information on areal features derived from the resting state network, myelin maps, and alignment of folding. The motivation for using MSM-All over MSM-

Sulc (cortical folding-based registration) came from previous studies that demonstrated a weaker correlation between sulcal depth and local curvature with regions responsible for higher cognitive functions, including Broca's area (Fischl et al., 2008; Van Essen, 2005), compared to the MSM-All registration, which showed improved cross-subject alignment of independent task fMRI datasets (Robinson et al., 2018).

Language Comprehension Laterality Quotient

Grayordinates localised regions-of-interest (ROIs) on the "inflated" brain surface (Van Essen & Glasser, 2016). A laterality quotient (LQ) was calculated to assess HLD for each participant's task fMRI activation using the CIFTI toolbox in MATLAB in ROIs associated with language comprehension. The analyses were conducted separately for frontal and temporal regions, given the well-documented phenomenon of crossed language dominance, where a participant may exhibit dominance in one hemisphere for frontal regions and the opposite hemisphere for temporal regions (Seghier, 2008). For the frontal ROIs, Brodmann areas 44 and 45 were selected due to their established high reliability in determining language dominance during semantic tasks (Sabbah et al., 2003; Seghier et al., 2008). In our temporal lobe laterality analyses, ROIs were chosen within the anterior temporal lobe (TGd, TGv, TE1a, TE2a, STGa, STSva, STSda) because these areas have been shown to be heavily involved in language comprehension (Binder et al., 2011) (Figure 1).

To work with CIFTI files, we generated *dscalar* files for each ROI using *wb_command*, imported them into MATLAB, and extracted z-values from ROIs using the CIFTI toolbox. The z-values were thresholded for each participant by including only grayordinates with values greater than the median in each ROI (Dietz et al., 2016). To account for the unequal number of grayordinates between the left and right hemisphere (approximately 100 more grayordinates on the left than the right), we corrected for these regional differences to ensure that comparisons between hemispheres were not skewed by differences in their sizes. This adjustment involved dividing the total sum of thresholded z-values by the number of grayordinates in each hemisphere for both frontal and temporal ROIs separately. The laterality

quotient (LQ) was then computed for each participant's normalised z-values using the equations below:

$$LQ = \frac{(L - R)}{\max\,(L, R)}$$

Where L represents the normalised z-values in the left, and R in the right ROI. We chose to employ an innovative LQ formula based on the Jaccard-Tanimoto index to provide a more sophisticated approach in evaluating and classifying language lateralisation (Seghier, 2019). This revised formula defines LQ as a metric of distance that adheres to a consistent distribution pattern, thus enhancing its sensitivity towards hemisphere activity differences, accentuating the distinctions between the two hemispheres. The values above +1/3 indicate left language dominance (LLD), values below -1/3 indicate right language dominance (RLD), and values between -1/3 and +1/3 indicate bilateral language representation (BLR), ensuring an equal cumulative probability in each dominance category.

Diffusion processing

Diffusion data was downloaded from the HCP S1200 Young Adult Data Release and preprocessed using the HCP Diffusion preprocessing pipeline using FMRIB diffusion toolbox in FSL. Briefly, the pipeline included b_0 image intensity normalisation, removing EPI susceptibility-induced field distortions with FSL's "topup" algorithm (Andersson et al, 2016), correcting for eddy current distortions, head movements, and gradient nonlinearities (Glasser et al., 2013). Quality control of the preprocessed diffusion MRI data was performed using DSI studio software (http://dsi-studio.labsolver.org). An automatic quality control routine then checked the b-table to ensure its accuracy (Schilling et al., 2019). The diffusion data were co-registered in MNI space using q-space diffeomorphic reconstruction (Yeh & Tseng, 2011) to obtain the spin distribution function (SDF) with a recommended length ratio of 1.25, as specified in the original study (Yeh et al., 2010) (Figure 2).

Connectometry analysis

We applied a whole-brain group connectometry analysis using DSI Studio as described in previous applications (Barnes-Davis et al., 2020, 2022; Dresang et al., 2021; Rahmani et al., 2017) to study the relationship between regional white matter quantitative anisotropy (QA) and language lateralisation measures derived from LQs (Figure 2). The connectometry approach derives the QA measure from the SDF in each fibre orientation, which defines the number of anisotropic spins along that direction in each streamline (Yeh et al., 2010, 2013). The anisotropy in each section of a white matter tract is then correlated with the study variable (Yeh et al., 2016). Unlike a voxel-based FA metric, which attributes identical anisotropy values to all fibre orientations within a voxel, QA demonstrates a discerning capability by identifying specific axonal orientations in each peak orientation of the SDF (Yeh et al, 2013).

Our connectometry analyses were conducted in two phases: the initial phase focused on examining the lateralisation of frontal regions during language comprehension, and the subsequent phase investigated temporal regions. Initially, connectometry analyses were performed on all participant groups concurrently, followed by post-hoc analyses on three distinct groups separately to aid in interpretation and capture varying effects related to different degrees of laterality. Specifically, the first post-hoc analysis included participants with LLD and BLR, the second consisted of participants with RLD and BLR, and the third included individuals with both LLD and RLD. The linear effect of handedness, sex, and age was mitigated using a partial linear correlation. A nonparametric Spearman partial correlation was used to derive the continuous segments correlating with a LQ (Yeh et al., 2016). Each reconstructed white matter tract within a voxel was tracked to extract a QA map for each participant (Yeh et al., 2013). A T-score threshold was assigned to the highest level of three to reduce the possibility of false positive results (Ashraf-Ganjouei et al., 2019). The tracks were filtered by topology-informed pruning with sixteen iterations to remove implausible spurious connections (Yeh et al., 2019). Given the large sample size in our study, and to prevent false positives, a conservative false discovery rate (FDR) correction for multiple comparisons was

employed with a threshold of 0.01 to select tracks showing significant associations between LQ and QA. To estimate the false discovery rate, 5000 randomized permutations were applied to the group label to obtain the null distribution of the track length. After the correlational results were obtained, additional categorical analyses were performed at the group level (LLD/RLD, LLD/BLR, RLD/BLR). Short tracts (<20mm) were removed for easier interpretation of our results.

Shape analysis

The SDF maps generated from the connectometry analysis were used for tract shape analysis and automatic fibre tractography was performed using a deterministic fibre tracking algorithm utilising DSI studio software (Yeh, 2020). Eleven white matter tract bundles that are part of language comprehension networks (Friederici et al., 2007; Harvey et al., 2013; Ivanova et al., 2021; Rollans & Cummine, 2018; Shin et al., 2019; Zhong et al., 2022; Forkel et al, 2022) were then automatically tracked and recognised based on the HCP-842 tractography atlas (Yeh et al., 2018) (Figure 3). These include the arcuate fasciculus (AF), corpus callosum body, corpus callosum forceps major (splenium), corpus callosum forceps minor (genu), inferior fronto-occipital fasciculus (IFOF), frontal aslant tract (FAT), inferior longitudinal fasciculus (ILF), the three branches of the superior longitudinal fasciculus (dorsal SLF1, middle SLF2 and ventral SLF3), and the uncinate fasciculus. All white matter bundles were independently tracked within the left and right hemispheres, while the corpus callosum bundles were tracked as a whole. The diffusion sampling length ratio was set at 1.25 and the output resolution was resampled to 2 mm isotropic. To remove false connections, topology-informed pruning was applied with 32 iterations (Yeh et al., 2019). We decided to exclude participants for whom we could not reconstruct at least one of their ROI bundles. As a result, 290 participants were excluded, leaving us with a final sample size of 750 participants. Finally, after identifying all white matter tracts of interest, the following shape metrics were extracted: tract length, span, curl, elongation, diameter, volume, and surface area were extracted (Figure 4).

To evaluate the statistical significance of differences among various laterality groups (LLD, RLD, BLR), we conducted an analysis of variance (ANOVA). This

analysis utilized the same laterality groupings based on frontal and temporal ROIs and included covariates consistent with those used in the connectometry analyses. All computations were performed using R (version 4.4.1).

Results

fMRI

Activations in frontal ROIs revealed a weak leftward lateralisation on the group level (LQ=0.33±0.31), while BOLD activations in anterior temporal lobe ROIs showed a more bilateral pattern (LQ=0.17±0.2). Based on the frontal ROIs of the fMRI language comprehension task, 581 participants were classified as left-hemisphere dominant (56%; LQ=0.53±0.16), 426 as bilateral (41%; LQ=0.13±0.17), and the remaining 33 as right-hemisphere dominant (3%; LQ=-0.64±0.17). For temporal ROIs, only 193 participants (19%; LQ=0.41±0.09) were left-hemisphere dominant, while 80% (n=833) were classified as bilateral (LQ=0.13±0.14). Only 14 participants (1%; LQ=-0.58±0.28) were right lateralised. In both laterality groups, strong neural activity is observed in brain areas associated with semantic processing i.e. anterior, and posterior temporal lobes as well as in the left inferior frontal gyrus (Jackson, 2021) (Figure 5). In line with previous reports that have used similar story/narrative materials, also the ventral angular gyrus bordering the temporoparietal junction was engaged during language comprehension (Lerner et al, 2011; Branzi et al, 2020; Branzi et al., 2021; Humbphreys & Lambon Ralph, 2015).

Connectometry

Two connectometry analyses were conducted. Firstly, in the investigation of language lateralisation in frontal regions, a total of 2028 white matter tracts exhibiting a significant negative correlation with LQ (n=1040; p<0.01, FDR corrected) were identified. Notably, the majority of these tracts were commissural, constituting 82% of the identified tracts, including the forceps minor (63%) and corpus callosum body (19%). A smaller portion of these tracts were positioned in bilateral fornix (18%). Conversely, 218 tracts were linked to higher frontal LQ values, all of which were situated in bilateral cingulum (n=1040; p<0.01, FDR corrected). Subsequently,

categorical post-hoc analyses were conducted to further illustrate the laterality groups influencing significant differences, with a specific focus on the disparities between LLD and BLR, RLD and BLR, and RLD and LLD. Within the cohort of bilateral and left lateralised individuals (n=1007), it was observed that individuals with left lateralisation exhibited higher QA in 2126 tracts, predominantly in the forceps minor (48%), corpus callosum body (38%), and bilateral fornix (8%), implying that the negative correlations in the primary findings were mainly driven by individuals with bilateral language dominance ($p<0.01$, FDR corrected). The remaining streamlines consisted of the right IFOF, right AF, and middle cerebellar peduncle (MCP). No tracts were found to be associated with left lateralised individuals. In the analysis encompassing individuals with bilateral and right hemisphere dominance (n=459), only 20 streamlines in the forceps minor exhibited higher QA in individuals with right hemisphere dominance compared to those with bilateral dominance ($p<0.01$, FDR corrected). No significant differences were observed between LLD and RLD (n = 614; $p<0.01$, FDR corrected).

The second connectometry analysis revealed a significantly negative correlation between anterior temporal lobe LQ and QA in 2,408 tracts (n=1040; $p<0.01$, FDR corrected). These tracts were predominantly located in the corpus callosum body (67%), with additional distributions in the left corticospinal tract (9%), left cingulum (7%), left medial lemniscus (5%), right dentarubrothalamic tract (3%), and bilateral AF (3%). Additionally, 118 tracts showed a positive correlation between QA and higher LQ in the anterior temporal regions, all of which were located in the forceps minor (n=1040; $p<0.01$, FDR corrected). Categorical post-hoc analyses found no significant differences between LLD and BLR (n=1029; $p<0.01$, FDR corrected) or between RLD and BLR (n=847; $p<0.01$, FDR corrected). However, LLD and RLD comparison (n=210) identified 391 streamlines with higher QA in RLD compared to LLD. These streamlines were distributed in the forceps minor (29%), corpus callosum tapetum (27%), bilateral arcuate fasciculus (26%), and right IFOF (8%).

Shape analysis

ANOVA analysis for language lateralisation in anterior temporal lobe showed that mean length of right IFOF was significantly different between three laterality groups (F_2 =9.8; p=0.005, FDR corrected). Tukey post-hoc tests showed that left lateralised individuals had longer right IFOF compared to people with BLR (p=0.01, FWE corrected). Another tract that showed significant difference was forceps minor, with different mean lengths between laterality groups (F_2=10.1; p=0.005, FDR corrected). Similarly, Tukey post-hoc tests showed that left lateralised people had longer forceps minor compared to bilateral individuals (p=0.01, FWE corrected) (Figure 7). No significant differences between frontal laterality groups were found in relation to shape metrics.

Discussion

Biological implications

We report significantly increased QA of the corpus callosum in individuals who had lower LQ in both frontal and temporal ROIs. Post-hoc analyses revealed that this result was driven by individuals with both BLR and RLD when laterality quotient was calculated using frontal regions, and by RLD when laterality quotient was based on the anterior temporal lobe. This observation aligns with prior research in patient cohorts (Tantillo et al., 2016) and supports the hypothesis that individuals who rely more on both cerebral hemispheres for language processing may have more developed commissural fibres. These fibres could potentially serve as a compensatory mechanism for the heightened metabolic energy requirements associated with information transfer and the reduction of transmission times (Laughlin & Sejnowski, 2003). An alternative hypothesis suggests that using both hemispheres for language processing is more natural than previously thought (Newport et al., 2022). This implies that the shift of language function towards the left hemisphere might result from less developed commissural tracts. Well-developed commissural tracts may facilitate bilateral language processing in frontal regions by allowing the right hemisphere to participate fully in language tasks (Newport et al., 2017). A higher forceps minor anisotropy in right lateralised people compared to people with LLD and BLR (Figures 6-1, 7-1) suggests that commissural tracts may

not necessarily enhance the function of both hemispheres but rather maintain right hemisphere involvement in language comprehension tasks.

Other imaging research has also suggested the importance of the corpus callosum for language lateralisation, although the link between structural measures of the corpus callosum and HLD is unclear. One study reported a greater FA of the whole corpus callosum in people with atypical language lateralisation (defined as RLD and BLR together) and, consistent with our results of anterior temporal lobe lateralisation, greatest anisotropy in people with RLD (Häberling et al., 2011). We found a positive correlation between a small segment of the left forceps minor and temporal LQ, suggesting a more complex role of the forceps minor than previously understood (Figure 6). This finding was supported by shape analysis, which revealed a longer forceps minor in individuals with left temporal language lateralisation. This aligns with a recent study using fixel-based analysis, which reported greater left fibre bundle cross-section asymmetry of the forceps minor in individuals with left language dominance (LLD) and higher asymmetry of the right forceps minor in those with RLD (Verhelst et al., 2021). Thus, while the body of the corpus callosum is associated with atypical (both bilateral and right) lateralisation for language comprehension in our study, the posterior and anterior parts of the corpus callosum are mainly associated with lateralised language, whether right or left, consistent with previous studies (Karpychev et al., 2022; Westerhausen et al., 2006). Although commissural fibres have shown relationships with language lateralisation in both previous and current studies, there is inconsistency regarding which individuals exhibit greater microstructural differences inferred by diffusion scalar metrics. This inconsistency may stem from methodological factors, such as the inclusion or exclusion of individuals with BLR and the type of language lateralisation assessed.

Our study reported a significant association between asymmetry in frontal activation and QA in the fornix bilaterally, particularly in individuals exhibiting an LQ closer to zero, indicating a more bilateral hemispheric representation. While there is limited existing literature on the relationship between HLD and diffusion measures in these tracts, some have highlighted the involvement of them in language processing (Hula et al., 2020; Sihvonen et al., 2021). Our findings related to temporal lobe laterality revealed a small number of streamlines in the AF bilaterally exhibiting higher anisotropy in individuals with RLD compared to LLD, but not in those with

BLR compared to LLD. This suggests that increased QA in these regions may be linked to right-hemisphere language lateralisation. Previous research has also found associations between AF asymmetry and language lateralisation in several cohorts of healthy individuals (Ocklenburg et al., 2013; Propper et al., 2010), although the exact relationship between AF asymmetry and HLD remains unclear (Gerrits et al., 2022; Verhelst et al., 2021). Further studies are needed to better understand these tracts' importance for language lateralisation.

Methodological considerations

To investigate the relationship between language lateralisation and white matter characteristics, we used both correlational methods and traditional categorical classifications (left, right, bilateral). Analysing raw LQ values for the entire sample helped reduce the subjectivity inherent in categorical groupings (Wegrzyn et al., 2019; Westerhausen et al., 2006). Instead of relying solely on global BOLD activation patterns to assess language lateralisation, we conducted two distinct studies focusing on the frontal and anterior temporal lobes. This approach allowed us to obtain more detailed insights. For instance, whilst lower LQs in both frontal and temporal regions were associated with increased anisotropy in the corpus callosum, frontal regions engaged a larger portion of the anterior corpus callosum body and the forceps minor. Interestingly, lower LQs in the temporal lobe were linked to increased anisotropy in the bilateral AF, which suggested a right hemisphere dominance, as indicated by post-hoc analyses—an effect not observed in the frontal lobe. Furthermore, while frontal LQs were positively correlated with fractional anisotropy in the bilateral cingulum, temporal LQs were associated with increased QA in the left forceps minor. Analysing language lateralisation separately for the frontal and temporal regions thus provided richer and more nuanced insights into the relationship between language comprehension and white matter characteristics.

The number of individuals with right hemisphere dominance, especially for anterior temporal region, is small in the present study compared to previous studies (Chang et al., 2011). This disparity is primarily attributed to the task used to assess HLD, which entailed semantic processing, resulting in more bilateral fMRI activations (Binder et al., 2011; Metoki et al., 2022; Walenski et al., 2019). This might be

because comprehension tasks rely less on the left-lateralised dorsal pathway, strongly associated with cognitive operations crucial for language production (e.g., retrieval and production of speech sounds) (Hickok & Poeppel 2007). Other non-mutually exclusive explanations include differences in the complexity of the linguistic stimuli (single words typically used in fluency tasks versus sentences typically used in comprehension tasks) and the demands that these tasks typically involve (see Peelle, 2012). For example, the verbal stimuli used for the stories likely portray social concepts (e.g., theory of mind, intention, emotion, morality) and/or they may contain different amounts of metaphor, idiom, or implied meaning. All these aspects have been associated with the recruitment of fronto-temporal and parietal regions in the right hemisphere (Miller et al. 1997; Olson et al. 2007; Yang, 2014; Schmidt et al., 2007).

The fact that we employed a language comprehension task might explain why only a small subset of participants demonstrated strong leftward lateralisation, while the majority displayed mild lateralisation. A recent systematic review comparing different language tasks has highlighted that language production tasks may be more robust in accurately assessing language laterality than language comprehension tasks (Bradshaw et al., 2017). For instance, there is evidence that between 6 and 24 years of age, there is an increase in frontal asymmetry during tasks involving the articulation of words. However, this asymmetry is not present during story listening. This suggests partly different maturational mechanisms between language comprehension and production (Lidzba et al., 2011; Berl et al., 2010). Future studies will have to use tasks that typically generate strongly left lateralised neural responses such as verbal fluency tasks to corroborate our findings.

Our methodology offers several practical benefits. Firstly, despite the limited proportion of right hemisphere dominant individuals identified through the functional language task, the sizeable sample size (N= 1040) employed in this study is the largest ever utilised in such investigations, thus potentially decreasing the likelihood of false positives. Secondly, we employed two complementary methodologies, namely connectometry and tractography, to delineate the precise white matter characteristics associated with HLD. In doing so, we have provided new insights into the anatomical basis of language lateralisation insomuch that white matter tract geometrical features (shape analysis) are unrelated to HLD at the group-level.

Conclusion

The findings of our study suggest that measures of diffusion-based microstructural architecture of reconstructed white matter tracts, are linked to language lateralisation. Specifically, individuals who exhibit a greater reliance on both cerebral hemispheres for language comprehension may possess more highly developed CC body fibres, thereby promoting more efficient interhemispheric communication. The involvement of anterior and posterior parts of the CC in asymmetrical temporal lobe activity (i.e., either left or right) for language comprehension unveils a more complex and nuanced role of the forceps minor. Future research should further investigate these relationships, employing tasks that typically generate strongly left-lateralized neural responses, to validate and expand upon our findings.

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Figure and table legends:

Figure 1. Regions of interest (ROIs) were selected to calculate LQ based on Jaccard-Tanimoto index (more details provided in text) (Seghier et al., 2019). The LQ value is expressed as a percentage, ranging from -1 to 1. Values greater than 1/3 indicate left-lateralization, values less than -1/3 indicate right-lateralization, and values between -1/3 and 1/3 indicate bilateral orientation (Seghier et al, 2019). TE1 – temporal area 1, found in middle temporal gyrus; STS – superior temporal sulcus; STG – superior temporal gyrus; TG – temporal gyrus; TE2 – temporal area, including ventral and dorsal parts of inferior temporal gyrus.

Figure 2. Flowchart of the methods pipeline. The pre-processed diffusion MRI data was reconstructed in an MNI space. The outputs of the reconstruction and SDFs were calculated to obtain the fibre orientations using DSI studio. Then, two different approaches were used to examine the white matter tracts associated with language laterality. The connectometry approach involved obtaining a local connectome matrix and finding out its association with LQ. Shape analysis involved the recognition of the WM tracts using HCP atlas and mapping eleven WM fibre bundles important for language function. The measures of key shape features, such as curl and volume, were extracted and linear regression analyses were used to look at the associations between shape metrics and LQ.

Figure 3. Eleven white matter tracts were reconstructed for shape analysis based on the HCP842 atlas computed on 1065 healthy people (Yeh et al, 2018).

Figure 4. Schematic illustration of the shape analysis of the white matter tracts. (a) The area metrics used in the included surface area (mm). (b) The length metrics used in the study included mean tract length (mm) as well as span bundle (mm) and diameter (mm) of the bundle. (c) The volume metrics used in the study included branch volume (mm3) (blue dotted line), trunk volume (mm3) (right dotted line), and total bundle volume (mm3) (black dotted line) (d) The shape metrics used in the study included curl and elongation.

Figure 5. Cohen's d maps of language comprehension task. The colour bar indicates Z scores; L – left hemisphere; R – right hemisphere**.**

Figure 6. Connectometry results for the language lateralisation in frontal lobe (n=1040). a) Tract sections negatively correlated with LQ ($p<0.01$, FDR corrected). b) Tract sections positively correlated with LQ ($p<0.01$, FDR corrected). Abbreviations: CC, corpus callosum. Colour bar represents t-statistic. See Extended Figure 6-1 for the group level posthoc analyses.

Figure 7. Connectometry results for the language lateralisation in temporal lobe (n=1040). a) Tract sections negatively correlated with LQ ($p<0.01$, FDR corrected). b) Tract sections positively correlated with LQ ($p<0.01$, FDR corrected). Abbreviations: AF -arcuate fasciculus; CC, corpus callosum; CS – corticospinal; DRT - dentatorubrothalamic. Colour bar represents t-statistic. See Extended Figure 7-1 for the group level posthoc analyses.

Figure 8. Violin plots (right) illustrating the mean length distribution in (a) the right IFOF and (b) the forceps minor (illustrated in left), across different temporal language lateralisation groups. Group differences are analysed using Tukey post-hoc tests, with adjustments for FDR. Significant differences are indicated by p-values less than 0.05 (FDR corrected), while non-significant differences are denoted by p-values greater than 0.05 (FDR corrected).

960 **Table 1**. A list of abbreviations used in this article.

Abbreviation	Definition
AF	Arcuate Fasciculus
ANOVA	Analysis of Variance
BLR	Bilateral Language Representation
BOLD	Blood-Oxygen-Level-Dependent Signal
CIFTI	Connectivity Informatics Technology Initiative Grayordinate Space
COPE	Contrast Of Parameter Estimates (COPE) Map
FDR	False Discovery Rate
FAT	Frontal Aslant Tract
FNIRT	a "medium resolution" non-linear registration method
FSL	The FMRIB Software Library
FWE	Family-Wise Error
fMRI	Functional Magnetic Resonance Imaging
HCP	Human Connectome Project
HLD	Hemispheric Language Dominance
IFOF	Inferior Fronto-Occipital Fasciculus
ILF	Inferior Longitudinal Fasciculus
LLD	Left Language Dominance
LQ	Laterality Quotient
MNI	Montreal Neurological Institute Space
MSM-ALL	Multimodal Surface Matching Registration
MSM-SULC	Cortical Folding-Based Registration
QA	Quantitative Anisotropy
ROI	Region Of Interest
RLD	Right Language Dominance
SDF	Spin Distribution Function

SLF	Superior Longitudinal Fasciculus
STGa	Superior Temporal Gyrus anterior
STSda	Superior Temporal Sulcus dorsal anterior
STSva	Superior Temporal Sulcus ventral anterior
TE1a	Temporal Area 1 anterior
TE2a	Temporal Area 2 anterior
TGd	Temporal Gyrus dorsal
TGv	Temporal Gyrus ventral

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