



# From structure to function in the lateralized brain: How structural properties of the arcuate and uncinate fasciculus are associated with dichotic listening performance

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## HIGHLIGHTS

- White matter tractography was related to dichotic listening performance.
- Structure of intrahemispheric white matter tracts was associated with functional lateralization.
- Arcuate and uncinate fasciculus had a larger tract volume in the left hemisphere.
- Volume of the left arcuate fasciculus was correlated to language asymmetry.
- Fractional anisotropy of the left arcuate fasciculus was correlated to language asymmetry.

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## ABSTRACT

Structural asymmetries in white matter tracts within the language system have been suggested to be one of the factors underlying functional language lateralization. To test this assumption, the present study examined how performance in the dichotic listening task, a behavioral measure of language dominance, is affected by macro- and microstructural properties of the arcuate and uncinate fasciculus. To this end, whole brain tractography was performed on 29 diffusion tensor imaging datasets obtained from healthy adult participants. Mean tract volume and fractional anisotropy of the uncinate and arcuate fasciculus were linked to the individual extent of the right ear advantage in the dichotic listening task. On the macrostructural level, both arcuate and uncinate fasciculus had a larger tract volume in the left compared to the right hemisphere. In contrast, fractional anisotropy was higher in the right than in the left arcuate fasciculus. These structural asymmetries were linked to functional lateralization, that is, tract volume and fractional anisotropy of the left arcuate fasciculus were positively correlated to the strength of functional language lateralization, as was the volume of the right uncinate fasciculus. In conclusion, the results of the present study suggest that both micro- and macro-structural properties of language-relevant intrahemispheric white matter tracts modulate the behavioral correlates of language lateralization.

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## 1. Introduction

Structural and functional brain asymmetries have been described in a large number of species within the Bilateria sub-regnum, both within the Protostomia [1] and the Deuterostomia [2]. In humans, one of the main foci of lateralization research is the language system and a left-hemispheric dominance has been described for most aspects of speech perception and production

[3]. One of the most widely used behavioral paradigms to assess language lateralization is the dichotic listening task [4,5]. In this paradigm, two different aural stimuli (e.g. tones, words, or syllables) are presented, one to the left and one to the right ear of the participant, at the same time. The participant's task then is to indicate which stimulus they heard best, and typically individuals report more right than left stimuli. While this so-called right-ear advantage is a well-documented behavioral correlate of left-hemispheric language dominance, its neuroanatomical basis is still not well understood. One of the major approaches to explain the ontogenesis of functional hemispheric asymmetries is the idea that they reflect underlying structural hemispheric asymmetries [6], and indeed dichotic listening performance has been linked to structural grey matter asymmetries, e.g. in the planum temporale [7]. However, this association is not found in all participants and has been shown to be modulated by sex and handedness [8]. In addition to grey matter asymmetries, structural asymmetries in language-relevant white matter pathways, e.g. the arcuate and uncinate fasciculus, have been suggested to be relevant for functional language lateralization [9]. In line with this argumentation, leftward structural asymmetries of the arcuate fasciculus (e.g. regarding fractional anisotropy or overall tract volume) have been linked to leftward activation asymmetries in a number of speech-related fMRI paradigms [10–12]. Whether or not structural white matter asymmetries affect behavioral measures of language lateralization, is however still unclear. The idea that structural properties of white matter tracts might influence performance in the dichotic listening task is supported by several studies linking micro- or macrostructural properties of the corpus callosum, the largest commissure in the human brain, to dichotic listening performance [13]. Moreover, it has been suggested that the efficacy of intrahemispheric fronto-temporal neural networks affects performance in this task [14]. However, to date the relation of intrahemispheric white matter asymmetries and dichotic listening performance has not been investigated experimentally. Thus, it was the aim of the present study to use diffusion tensor imaging (DTI) to elucidate the question, how micro- and macrostructural properties of the left and right arcuate and uncinate fasciculus are related to functional language lateralization. Based on previous studies [4,5] we expect our participants to show a clear right-ear advantage in the dichotic listening task. We also expect the arcuate and uncinate fasciculus to show leftward asymmetries on both the micro- and macrostructural level [9–12]. Moreover, we expect the structural properties of the two fasciculi to be significantly correlated with the extent of the right-ear advantage in the dichotic listening task.

## 2. Materials and methods

### 2.1. Participants

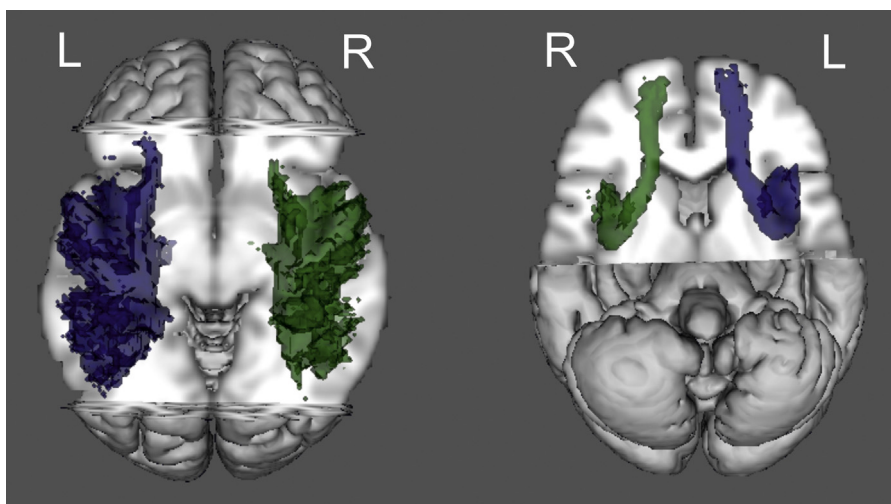
The participants were 29 neurologically healthy adult Norwegians (mean age: 21.7 years; S.E.M.: 0.42; 15 women, 14 men) with normal hearing capabilities on both ears as determined by audiometry. Since it is known that handedness might affect dichotic listening performance [15], handedness was determined using a Norwegian version of the Edinburgh Handedness Inventory [16] and only right-handed participants were included in the study cohort (all laterality quotients were larger than +40). The study was approved by the Regional Committee for Medical Research Ethics of Western Norway (REK-vest). All participants were treated in accordance with the declaration of Helsinki. Before the start of the experiment they were informed about the aims and methods of the studies and informed consent was acquired before starting the experiment.

### 2.2. Dichotic listening task

This task was based on the classic dichotic listening task [4,5]. Six different consonant-vowel syllables (/ba/, /da/, /ka/, /ga/, /pa/, /ta/) with a mean duration of approximately 350–400 ms were used as stimuli. The syllables were presented dichotically over headphones (two different syllables at the same time, one in each ear) using E-Prime® software (Psychology Software Tools, Inc., Sharpsburg, USA). Overall, there were 30 different dichotic consonant-vowel syllable combinations pairs. Subjects were instructed to report orally which of the two syllables he or she heard after each trial. Responses were written down by the experimenter and also recorded as an mp3-file using a microphone and an audio recorder for later confirmation. Overall, the task consisted of 90 experimental trials (each of the 30 possible syllables was presented three times) in randomized order. In order to get a quantitative measure of the individual magnitude and direction of language lateralization, a laterality index (LI) was calculated for each participant. The formula to calculate the LI was  $LI = [(RE - LE) / (RE + LE)] \times 100$ , with RE indicating the number of right-ear stimuli reported and LE the number of left-ear stimuli reported. The LI can take values between -100 (100% left ear reports) to +100 (100% right ear reports) with 0 indicating that the number of left- and right-ear stimuli reported be the participant was identical.

### 2.3. Image acquisition and tractography

Magnetic resonance (MR) imaging was performed on a 3 Tesla General Electric Medical Systems Signa scanner, located at the Haukeland University Hospital (Bergen, Norway). The MR scanning protocol started with a 3D survey scan that was followed by an anatomical and a DTI sequence. The anatomical T1-weighted images were acquired using Fast Spoiled Gradient Recall (FSPGR) acquisition scheme (echo time: 3.1 ms; repetition time: 7.9 ms; flip angle: 11°) to obtain 180 consecutive sagittal slices (scan matrix: 256 × 256; field of view: 256 × 256 mm; slice thickness: 1 mm). Diffusion weighted imaging was performed using an array spatial sensitivity encoding technique (ASSET) based on a single-shot echo-planar imaging sequence with an echo time of 89 ms and a flip angle of 90°. The acceleration factor was 1 and diffusion-sensitizing gradients were applied in 30 directions with a weighting factor of  $b = 1000 \text{ s/mm}^2$ . Moreover, six reference images ( $b = 0 \text{ s/mm}^2$ ) were acquired. The diffusion-sensitization directions were based on an established sampling scheme [17] that has been proven to yield a robust reconstruction of the diffusion tensor and reliable estimation of anisotropy parameters. The measurement volume covered the entire brain. Overall, it consisted of 45 contiguous axial slices (thickness: 2.4 mm; field of view: 220 mm × 220 mm; scan matrix: 128 × 128; reconstructed voxel size: 1.72 mm × 1.72 mm × 2.4 mm). Tensor estimation and tractography was conducted using the Matlab®-based version of ExploreDTI® 4.8.2 (<http://www.exploredti.com/>) [18]. First, individual DICOM-files were converted to Nifti-files using the DCM2NII converter plug-in for ExploreDTI. After creation of the b-matrix, non-linear diffusion tensor estimation with 36 directions was conducted (voxel size: 1.72 mm × 1.72 mm × 2.4 mm). The obtained data were visually inspected and checked for correct orientation. Subsequently, images were corrected for motion and distortion and transformed to MNI space [19]. Using these diffusion weighted images that were transformed to MNI space, whole brain tractography was performed. In order to reconstruct the left and right uncinate fasciculus, a multiple region of interest approach based on the location of these tracts according to a widely used diffusion tensor imaging tractography atlas [20] was used and automated atlas based tractography [21] was performed. For each participant, the left and right arcuate and uncinate fasciculus were tracked and



**Fig. 1.** Average tractography results for the left (blue) and right (green) arcuate fasciculus (left side) and the left (blue) and right (green) uncinate fasciculus (right side). Average tracts were thresholded to include only voxels in which at least 5 out of 29 participants had a pathway. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

for each of these structures, mean tract volume (TV) was assessed as a macrostructural measure and mean fractional anisotropy (FA) as a measure of its microstructural properties. All statistical analyses were conducted using IBM® SPSS® Statistics version 22.

### 3. Results

#### 3.1. Dichotic listening

The dichotic listening data were analyzed using a  $2 \times 2$  repeated measures ANOVA, with ear (left, right) as within-subjects factor and participants' sex as between-subjects factor. On average, participants reported significantly more syllables presented to the right ear (37.41; SD = 8.88) as compared to the left ear (20.52; SD = 6.68; main effect ear:  $F_{(1,27)} = 42.44$ ;  $p < 0.001$ ), reflecting the well-known right-ear advantage in this task. Both the main effect sex ( $p = 0.63$ ) and the interaction ( $p = 0.26$ ) failed to reach significance. The mean LI was 28.7 (SD = 21.67), also indicating a right-ear advantage (one-sample  $t$ -test against a test value of 0:  $t_{(28)} = 7.04$ ,  $p < 0.001$ ). The LI's were normally distributed (one-sample Kolmogorov–Smirnov test,  $p = 0.2$ ).

#### 3.2. DTI

Structural left-right asymmetries in the uncinate and arcuate fasciculus (see Fig. 1) were determined by comparing left- and right-sided fasciculi using within samples  $t$ -tests. For the uncinate fasciculus, a significant left ( $3.52 \text{ cm}^3$ ; SD =  $1.27 \text{ cm}^3$ ) larger than right ( $2.62 \text{ cm}^3$ ; SD =  $1.56 \text{ cm}^3$ ) difference was observed for approximate tract volume ( $t_{(28)} = 2.84$ ;  $p < 0.01$ ), while FA failed to reach significance (left: 0.449; SD = 0.022; right 0.448; SD = 0.022;  $t_{(28)} = 0.11$ ;  $p = 0.92$ ). For the arcuate fasciculus, a comparable left ( $27.09 \text{ cm}^3$ ; SD =  $7.11 \text{ cm}^3$ ) larger than right ( $23.66 \text{ cm}^3$ ; SD =  $5.43 \text{ cm}^3$ ) difference was observed for approximate tract volume ( $t_{(28)} = 3.63$ ;  $p < 0.001$ ), while FA was higher in the right (0.461; SD = 0.017) compared to the left (0.454; SD = 0.015) arcuate fasciculus ( $t_{(28)} = -2.34$ ;  $p < 0.05$ ).

#### 3.3. Relation of structural and behavioral hemispheric asymmetries

To investigate the relation between structural asymmetries in the uncinate and arcuate fasciculus and functional language

**Table 1**

Neyman–Pearson correlation coefficients between mean approximate tract volume in  $\text{mm}^3$  and mean fractional anisotropy of the left and right uncinate fasciculus and arcuate fasciculus and laterality index (LI) as well as left and right ear score in the dichotic listening (DL) test.

	DV	Tract volume	Fractional anisotropy
Left uncinate fasciculus	DL LI	0.24	0.32
	DL left ear	-0.17	-0.31
	DL right ear	0.33	0.31
Right uncinate fasciculus	DL LI	0.49**	0.34
	DL left ear	-0.42*	-0.25
	DL right ear	0.57**	0.39 <sup>†</sup>
Uncinate fasciculus LI	DL LI	-0.25	-0.02
	DL left ear	0.23	-0.06
	DL right ear	-0.25	-0.1
Left arcuate fasciculus	DL LI	0.37*	0.37 <sup>†</sup>
	DL left ear	-0.34	-0.27
	DL right ear	0.35	0.47 <sup>†</sup>
Right arcuate fasciculus	DL LI	0.32	0.27
	DL left ear	-0.28	-0.10
	DL right ear	0.30	0.45 <sup>†</sup>
Arcuate fasciculus LI	DL LI	0.1	0.15
	DL left ear	-0.09	-0.22
	DL right ear	0.08	0.08

Note:

<sup>†</sup>  $p < 0.05$ .

\*\*  $p < 0.01$ .

lateralization, Neyman–Pearson correlation coefficients were calculated between the structural measures (tract volume and fractional anisotropy) and the right and left ear performance in the dichotic task, as well as the dichotic listening LI (see Table 1).

For the arcuate fasciculus, there was a significant positive correlation between tract volume ( $r = 0.37$ ;  $p < 0.05$ ) and fractional anisotropy ( $r = 0.37$ ;  $p < 0.05$ ) of the left arcuate fasciculus and the laterality index obtained from the dichotic listening task. At least for fractional anisotropy, this effect seemed to be driven by an increase in right ear score, as indicated by a significant positive correlation between FA and right ear score ( $r = 0.47$ ;  $p < 0.05$ ). Interestingly, a similar effect was also observed for the right arcuate fasciculus ( $r = 0.45$ ;  $p < 0.05$ ). For the uncinate fasciculus, larger tract volume in the right hemisphere was related to a stronger right ear advantage in the dichotic listening test ( $r = 0.49$ ;  $p < 0.01$ ). This effect was

due to both an increase in right ear performance and a decrease in left ear performance with increasing tract volume, as indicated by a negative correlation between right uncinate tract volume and left ear score ( $r = -0.42$ ;  $p < 0.05$ ) and a strong positive correlation between right uncinate tract volume and right ear score ( $r = 0.57$ ;  $p < 0.01$ ). Comparably, higher mean fractional anisotropy of the right uncinate fasciculus was also related to a significantly higher right ear score ( $r = 0.39$ ;  $p < 0.05$ ). No relations between structural properties of the left fasciculus and functional lateralization were observed.

#### 4. Discussion

Performance in the dichotic listening task reflects the extent of left-hemispheric language dominance and has repeatedly been shown to be related to structural properties of language-relevant brain regions, e.g. the planum temporale [7], and the corpus callosum [13]. While some authors proposed the idea that structural properties of language-relevant white matter pathways, e.g. the arcuate and uncinate fasciculus, might be relevant for functional language lateralization [9], this assumption has so far not been experimentally tested with behavioral performance measures of language lateralization, such as the dichotic listening task. In accordance with previous studies, we observed that participants on average reported significantly more syllables presented to the right ear than to the left ear. This phenomenon has been termed right-ear advantage [4,5] and is thought to reflect left-hemispheric language dominance. Despite the overall right-ear advantage, dichotic laterality indices showed considerable interindividual variation and were normally distributed, making a meaningful analysis of structure–function relationships possible. Regarding macrostructural asymmetries, we found that both fasciculi had a significantly larger overall tract volume in the left, compared to the right hemisphere, a finding in line with previous studies that reported leftward volume asymmetries of the arcuate [10,22] and uncinate fasciculus [23]. Besides tract volume, FA was assessed as a measure of microstructural fiber integrity. Higher FA has been related to more axons, stronger myelination, and thicker axon diameter, which could be reflected in better or faster neuronal information transfer between the connected regions [24]. We found no left–right asymmetries for the uncinate fasciculus, but the arcuate fasciculus showed higher FA on the right than on the left side. While this finding is in line with some studies [25], others also report a leftward FA asymmetry in the arcuate fasciculus [26]. Regarding the relationship between structural properties of the two fasciculi and functional language lateralization, Barrick et al. [9] suggested a close association between language-related white matter pathway organization and lateralized brain function. This suggestion is indeed supported by the present results. For the arcuate fasciculus we found a positive relationship between both left tract volume and fractional anisotropy and laterality index in the dichotic listening task. Thus, participants with a larger and structurally more coherent left arcuate fasciculus also had stronger functional asymmetry. This finding is in line with a previous neuroimaging study by Powell et al. [10], who reported a significant positive lateralization of mean arcuate fasciculus FA and leftward lateralization of frontal fMRI activation during verb generation and temporal activation during reading comprehension. Other neuroimaging studies showed an influence of handedness on the relation between structural white matter asymmetries and functional language lateralization. For example, Vernooij et al. [12] showed that in right-handers, but not in left-handers, regional fiber density asymmetry of the arcuate fasciculus was positively related to fMRI activation asymmetry during verb generation. In contrast, Propper et al. [11] found less clear results, with an fMRI activation lateralization in Wernicke's area being positively related to arcuate fasciculus volume

in consistent-left-handers, but not in other participants. These contrasting results might be due to methodological differences between the two studies, as well as sample characteristics. The arcuate fasciculus connects Broca's area to Wernicke's area, as well as a number of other speech-relevant structures in the frontal, temporal, and parietal lobes [27]. While it is not clear, what causes the larger left than right volume of the arcuate fasciculus, possibilities include a higher number of axons, a larger average axon diameter, or thicker myelination of axons in the left compared to the right arcuate fasciculus. Thus, one can assume that a larger tract volume leads to more efficient and/or faster neuronal information transport between different subregions of the language system within the left hemisphere. A similar reasoning can be brought forward regarding the finding that greater mean FA of the left arcuate fasciculus was linked to stronger language lateralization, since FA has been linked to axon packing and myelination, with an increase in FA being observed with increasing myelination [28]. Increased brain efficacy (i.e. less energy consumption per cognitive operation) has been proposed to be one of the major evolutionary advantages of lateralization [29]. Thus, our results would indicate that a stronger efficacy gain in left-hemispheric language networks due to an increased leftward lateralization of the arcuate fasciculus, would result in stronger behavioral leftward lateralization, as observed in the dichotic listening results. This idea is also supported by studies investigating the role of interindividual variability in the corpus callosum for dichotic listening performance. Interestingly, it has been found that a stronger connection between the two hemispheres results in reduced language lateralization [13]. Thus, while an increased efficacy of the left arcuate fasciculus leads to increased lateralization, increased efficacy of the corpus callosum (resulting in faster information exchange between the hemispheres) has the opposite effect, since it reduces the evolutionary advantage of a strong asymmetry in unihemispheric performance.

For the uncinate fasciculus, overall tract volume in the right, but not in the left hemisphere was related to increased lateralization in the dichotic listening task, an effect that was due to both an increase in right ear performance and a decrease in left ear performance with increasing tract volume. Also, FA of the right but not the left fasciculus was positively correlated with right ear performance and there was a trend towards a positive correlation for lateralization in the dichotic listening task. Thus, somewhat unexpectedly, micro- and macrostructural properties of the right, but not the left, uncinate fasciculus were associated with functional language lateralization. The uncinate fasciculus connects the anterior temporal lobe with the inferior frontal lobe [23]. Thus, a larger and structurally more coherent connection between these areas in the non-dominant right hemisphere increases leftward language lateralization. Functionally, the uncinate fasciculus has been linked to memory [30], emotional regulation [31] and negative emotionality [32]. Within the language system, its main function has been related to naming, for example, of people and objects [33]. Our results suggest that the right uncinate fasciculus might play a role in enhancing functional lateralization by reducing interference from the non-dominant right hemisphere. Interestingly, it has been shown that the corpus callosum, the large white matter pathway connecting the two hemispheres, has inhibitory in addition to excitatory influences on the contralateral hemisphere and that the strength of inhibitory connections possibly modulates functional lateralization [34]. One could speculate that the uncinate fasciculus might play a role in transferring inhibitory information the temporal lobe receives via the corpus callosum to frontal speech region, but clearly more research is needed before any conclusions can be drawn on this question. Interestingly, it has been found that depressed women show both a lower FA in the right uncinate than healthy controls [35] and a reduced right-ear advantage in the dichotic listening task [36], making the uncinate fasciculus an

interesting candidate region for future clinical studies investigating the relation of structural and functional asymmetries in mood disorders.

In summary, the present study provides evidence that both micro- and macro-structural properties of language-relevant intrahemispheric white matter tracts modulate the behavioral correlates of language lateralization. For future research it would be especially interesting to investigate how this relationship is modulated by structural properties of the corpus callosum, since interhemispheric transfer has been shown to be highly relevant for performance in the dichotic listening task. Moreover, the dichotic listening task mainly assesses hemispheric asymmetries in phonemic and phonological processing. Thus, it would be interesting for future studies to see if the results of the present study could be replicated with task that assess other aspects of language, e.g. semantic or syntactic processes. Also, more research on the functional relevance of the uncinate fasciculus for language lateralization is needed.

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