



Leftward asymmetry in relative fiber density of the arcuate fasciculus

Paolo G. P. Nucifora,^{1,CA} Ragini Verma,¹ Elias R. Melhem,¹ Raquel E. Gur² and Ruben C. Gur²

¹Departments of Radiology; ²Psychiatry, University of Pennsylvania, Philadelphia, PA 19104, USA

^{CA}Corresponding Author: nucifora@rad.upenn.edu

Received 28 January 2005; accepted 2 March 2005

Left hemispheric language dominance is well established, but the structural substrate for this functional asymmetry is uncertain. We report a strong asymmetry in the relative fiber density of the arcuate fasciculus, a white matter pathway associated with language that connects the frontal, temporal, and parietal lobes. Measured with diffusion tensor tractography, nearly all study participants demonstrated greater relative fiber density in the left

arcuate fasciculus than in the right arcuate fasciculus. In comparison, we found no asymmetry in the corticospinal tract, an important white matter pathway with no known role in language. Combined with data on volumetric and activation asymmetry, greater connectivity may provide the elements of a neural system model for language lateralization. *NeuroReport* 00:000–000 © 2005 Lippincott Williams & Wilkins.

Key words: Arcuate fasciculus; Diffusion magnetic resonance imaging; Neural pathways; Pyramidal tracts

INTRODUCTION

In our daily activities, nearly all of us demonstrate a preference for one hand over the other, a puzzling phenomenon in light of the brain's superficial symmetry. A fundamental asymmetry of the two hemispheres was first described by Broca, who noted that lesions affecting language usually localized to the left hemisphere [1]. This functional asymmetry is now considered to include general classes of information processing, with greater left hemispheric involvement in the verbal, analytic, and temporal domain, whereas processing of spatial and spectral information occurs in the right hemisphere [2]. Many studies from the early days of functional imaging have shown reliably greater activation of left hemispheric regions for verbal and right hemispheric regions for spatial tasks [3], yet structural asymmetries have been less clearly demonstrated. Nonetheless, a growing body of evidence suggests that this functional asymmetry may have a structural substrate.

Early evidence from ¹³³Xe clearance studies suggested a higher percentage of gray matter in the left hemisphere, especially in temporal regions [4]. These asymmetries have been confirmed with magnetic resonance imaging (MRI) [5]. In the temporal lobe, specifically, the left planum temporale is larger than the right [6], and the degree of activation detected during a language task is a function of the size of the left planum temporale [7]. Handedness may also be related to the relative sizes of the central sulci [8]. The relationship between structure and function in the brain is still unclear, but recent evidence suggests that white matter organization may play an important part in the functional asymmetry of the brain. White matter volumes are asymmetric in the temporoparietal regions associated with language [9]. Increased ratio of white matter to gray matter

in the left parietal lobe has been correlated to improved performance on a language task [10], while right hemispheric white matter volume has been associated with better performance on spatial tasks [11].

Diffusion tensor magnetic resonance imaging (DT-MRI) is a relatively new imaging technique based on measuring water diffusivity in the brain tissue and provides an excellent characterization of white matter [12]. Water diffusivity is considerably more anisotropic (directional) in white matter than in gray matter, probably owing to an arrangement of axonal membranes and microstructural components that inhibit motion perpendicular to the orientation of the axon. By applying multiple directional motion probing gradients, DT-MRI can be used to quantify this anisotropy of water diffusivity and provide a useful assessment of the microstructural integrity of white matter. In DT-MRI, each voxel has an associated tensor that specifies the magnitude (eigenvalues) and orientation (eigenvectors) of the diffusivity of water. Diffusivity-based measures derived from these tensors are used to characterize white matter. For example, fractional anisotropy (a scalar measure of anisotropy) is decreased in the temporal–parietal white matter of patients with reading disorders [13]. The utility of DT-MRI can be extended by using the directional information in the diffusion tensor to generate fiber tracts. This technique allows the direct visualization of the anatomy of known white matter pathways, with excellent correspondence to conventional dissection [14–17].

We used fiber tracking in healthy people to examine the arcuate fasciculus, a pathway that has long been associated with language [2]. Connecting the frontal, parietal, and temporal lobes, the arcuate fasciculus was thought to be responsible for the functional relationship between speech

production (in the frontal and anterior parietal lobes) and speech perception (in the temporal lobe). It was originally described by Carl Wernicke, who proposed that lesions to this pathway would cause a specific type of aphasia, 'conduction aphasia', with features distinct from motor or receptive aphasia. Although patients with conduction aphasia have been identified, it is still unclear whether their symptoms are due to white matter dysfunction, cortical dysfunction, or a combination of both [18]. Consequently, the role of the arcuate fasciculus in language is still not well understood. Through our analysis of the arcuate fiber tracts using DT-MRI fiber tracking, we demonstrate a significant left-dominant asymmetry that may provide the foundation for future functional and structural studies.

MATERIALS AND METHODS

Study participants: Written informed consent was obtained from 27 medically healthy volunteers (14 men and 13 women), with no history of any disorder affecting brain function. All participants were right-handed, as assessed by questionnaire [19]. The protocol for this study was approved by an institutional review board.

Data acquisition and analysis: DT-MRI was performed with a 3.0T Siemens scanner using 12 motion probing gradients [12]. DT-MRI data were acquired using single-shot spin-echo-type echo planar imaging, with the following parameters: repetition time of 6500ms, flip angle of 90°, echo time of 99ms, *b* factor of 800s/mm². Images were acquired using a 22 cm field of view onto a 128 × 128 matrix, with 3-mm-thick axial slices.

Fiber tracking was performed with the free software Diffusion TENSOR Visualizer II (University of Tokyo Hospital, Tokyo, Japan) using the continuous tracking (FACT) method described by Mori and van Zijl [16] and Masutani *et al.* [17]. In addition, a semiautomated method was used to define the seed regions of interest (ROIs) in order to exclude extraneous white matter tracts and gray matter. First, one to five voxels were selected interactively on the directionally encoded tensor map in either the deep white matter of the posterior parietal lobe (arcuate fasciculus) or the cerebral peduncle (corticospinal tract). The principal eigenvector for each voxel in the ROI was then compared with that of each adjacent voxel that was not in the ROI. The adjacent voxel was added to the ROI if the two vectors subtended an angle less than 10°. This process was iterated until the seed ROI contained a total of 70–100 voxels. The target ROI was constructed in the same manner, except that the process was continued until the target ROI contained a total of 1000–1100 voxels, and the initial voxels were selected in the deep white matter of the posterior temporal lobe (arcuate fasciculus) or posterior limb of the internal capsule (corticospinal tract).

Approximately 600–800 subvoxel points were randomly generated within the seed ROI, and a fiber track was extended bidirectionally from each point following the pathway of greatest diffusion until it entered a voxel with fractional anisotropy below 0.18, indicating it had probably reached gray matter. Using the two-region method, the three-dimensional fiber tracts were then classified into arcuate tracts and nonarcuate tracts on the basis of whether they had passed through a predefined target in the posterior

temporal lobe [15]. The structure of the fiber tracts was visually inspected and was always in keeping with known white matter anatomy; any fiber track that extended posterior to the fourth ventricle was considered part of the cerebellar circuit and therefore excluded when evaluating the corticospinal tract.

In order to normalize the size of the ROIs and the fiber tracts across participants, a new measure, *relative fiber density*, was defined as $N_{\text{arcuate}}/N_{\text{total}}$ (the ratio of the number of arcuate tracts to the total number of fiber tracts generated in the arcuate ROI). Similarly, the corticospinal tract, a separate pathway involved in descending control of motor function, was quantified with $N_{\text{corticospinal}}/N_{\text{total}}$ (the ratio of the number of corticospinal tracts to the total number of fiber tracts generated in the corticospinal ROI). The corticospinal tract is not believed to be involved in lateralized tasks such as language, and thus the relative fiber density of the corticospinal tract was used for control purposes.

Statistical comparisons were performed using the Student's *t*-test for independent samples (two-tailed).

RESULTS

Figure 1a and b superimposes fiber tracking of the arcuate fasciculus and corticospinal tract on a T2-weighted parasagittal image of a representative participant. The arcuate fasciculus, displayed in red, extended from the posterior frontal lobe, through the parietal lobe, and then curved inferiorly toward the posterior temporal lobe. Nonarcuate fiber tracts (not shown) were heterogeneous and often entered the occipital lobe or crossed the midline via the corpus callosum. For this individual, the relative fiber density of the arcuate fasciculus on the left side, 0.29 (a), was more than an order of magnitude greater than the relative fiber density on the right side, 0.02 (b). This example of evident white matter asymmetry, in a region of the brain known to support language, can be used to establish the link between local function and underlying white matter structure.

The corticospinal tracts, displayed in yellow, extended inferiorly from the region of the central sulcus to the cerebral peduncles and then continued into the brainstem. In this individual, the corticospinal tracts were much less asymmetric (left relative fiber density=0.12, right relative fiber density=0.32), which is to be expected given the known symmetry in cortical control of motion.

The diffusion tensors calculated for the same participant are illustrated in Fig. 1c. The color map indicates the overall direction of white matter fibers in the surrounding volume. In regions of gray matter, diffusion is much less anisotropic and the diffusion tensor is not represented. No gross asymmetry was observed between the left hemisphere and the right hemisphere. The white matter volume surrounding the arcuate fasciculus, * in Fig. 1c, did not exhibit the degree of asymmetry seen in the fiber tracts. This probably reflects the presence of multiple white matter tracts in the same volume with different degrees of asymmetry, demonstrating the advantages of fiber tracking in the isolation and characterization of specific white matter pathways. Furthermore, these axial images are based only on the information contained within a particular voxel. In contrast, the properties of a fiber track through a voxel depend on signals from multiple regions, as the track represents the connectivity of

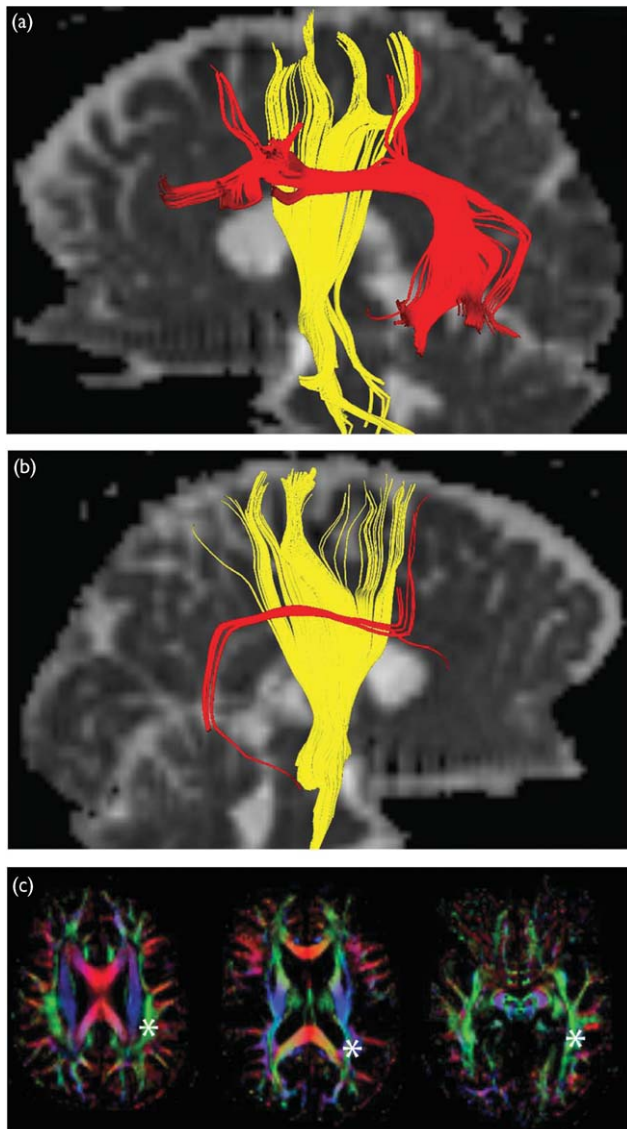


Fig. 1. Reconstructions of left (a) and right (b) arcuate fasciculus (red) and corticospinal tract (yellow) from a representative participant are superimposed on a parasagittal T2-weighted image. Note that fiber tracts are represented with stream tubes to improve visibility; only one sample is rendered of the 600–800 fiber tracts generated. (c) Axial sections from a representative participant, indicating the direction of the principal eigenvector of diffusion (red=medial–lateral, blue=superior–inferior, green=rostral–caudal). The approximate location of the left arcuate fasciculus is indicated by *.

a voxel to the rest of the brain. Fiber tracking effectively ‘incorporates signal distal to the ROI’ [16].

The fiber track density of the arcuate fasciculus was significantly greater on the left side than on the right. The average arcuate relative fiber density was 0.41 ± 0.04 on the left side, and 0.12 ± 0.02 on the right side ($p < 0.001$). The asymmetry index, defined as $(\text{Density}_{\text{left}} - \text{Density}_{\text{right}}) / (\text{Density}_{\text{left}} + \text{Density}_{\text{right}})$, may be used to quantify the degree of asymmetry for each participant (values range from -1 to $+1$; positive values indicate leftward asymmetry, negative values indicate rightward asymmetry). The mean asymmetry index of the arcuate fasciculus was 0.62 . In all

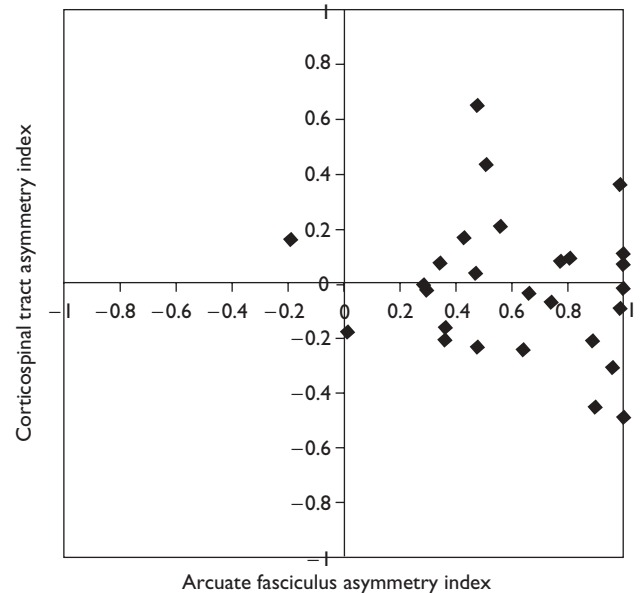


Fig. 2. The asymmetry index of arcuate fasciculus is plotted against the asymmetry index of the corticospinal tract for each participant. The arcuate fasciculus demonstrates strong leftward asymmetry, whereas the corticospinal tract does not. No clear relationship exists between corticospinal asymmetry and arcuate asymmetry.

but one participant, the asymmetry index of the arcuate fasciculus was positive. The single participant with rightward asymmetry had a psychological profile that was similar to the other participants, and probably represents a normal variant. In 16 of 27 participants, the asymmetry index was greater than 0.50 , and in four of them the asymmetry index was 1 (i.e. the right-sided arcuate fibers were below the threshold of detection).

In contrast to the arcuate fasciculus, the corticospinal tract was relatively symmetric. The mean relative fiber density of the corticospinal tract was 0.31 ± 0.03 on the left side and 0.34 ± 0.03 on the right side, not a significant difference. The mean asymmetry index of the corticospinal tract was -0.01 . The asymmetry index of the corticospinal tract was positive in 11 participants and negative in 16 participants. Figure 2 compares the asymmetry indices of the arcuate fasciculus and the corticospinal tract for each participant. Even when strong leftward asymmetry was found in the arcuate fasciculus, a normal distribution of asymmetry was observed in the corticospinal tract. The lack of a strong relationship between asymmetry in the arcuate fasciculus and asymmetry in the corticospinal argues against an overall hemispheric asymmetry. Rather, asymmetry must be determined separately for each white matter tract.

DISCUSSION

Increasing evidence exists for asymmetry in white matter structure throughout the brain, including increased white matter volume in the left temporal lobe [9]. Using DT-MRI, increased relative anisotropy has been found in the left subinsular white matter [20]. A voxelwise analysis of fractional anisotropy showed leftward asymmetry in the superior uncinata fasciculus but rightward asymmetry in the inferior uncinata fasciculus [21]. Finally, Buchel *et al.* [22]

showed leftward asymmetry in regions of temporal white matter containing the arcuate fasciculus. However, multiple white matter tracts potentially exist within any given brain volume, complicating a voxel-based analysis of structural asymmetry. In our study, for example, short cortical association fibers accounted for a large number of the white matter tracts found even in a well defined volume. The short cortical association fibers may not have the same degree of asymmetry as the longer tracts that they overlap. Separating them from the white matter tract of interest requires information regarding the entire course of the fiber, which is only obtained through a procedure such as fiber tracking.

Because language processing requires participation of a distributed neural system in the left hemisphere [23], the present finding of greater connectivity in the language areas of the left hemisphere provides a possible structural substrate for the functional asymmetry. Measurement of the relative fiber density of the arcuate fasciculus may prove useful in the study of language disorders such as dyslexia, where interregional connectivity has been implicated [24]. Such measures could also be useful for understanding conduction aphasia. An association between the severity of aphasia and diminished relative fiber density would support a role for the arcuate fasciculus in this disorder. Furthermore, decreased white matter asymmetry in the temporal lobe has been associated with stuttering [25]; determination of the degree to which this involves the arcuate fasciculus may prove helpful in identifying causes of this and other communicative disorders.

CONCLUSION

This study builds on reports of local microstructural differences in the left and right hemispheres and compares the overall fiber densities of the entire left and right arcuate fasciculi. Greater relative fiber density is found in the left arcuate fasciculus than in the right arcuate fasciculus in nearly all participants. Remarkably, this strong degree of asymmetry is specific to the arcuate fasciculus, as the corticospinal tract is symmetric. This was further demonstrated by the lack of asymmetry in whole-brain tensor maps. This asymmetric connectivity may provide the neural substrates for hemispheric language organization.

REFERENCES

- Berker EA, Berker AH, Smith A. Translation of Broca's 1865 report. Localization of speech in the third left frontal convolution. *Arch Neurol* 1986; **43**:1065–1072.
- Hutsler J, Galuske RA. Hemispheric asymmetries in cerebral cortical networks. *Trends Neurosci* 2003; **26**:429–435.
- Gur RC, Reivich M. Cognitive task effects on hemispheric blood flow in humans: evidence for individual differences in hemispheric activation. *Brain Lang* 1980; **9**:78–92.
- Gur RC, Packer IK, Hungerbuhler JP, Reivich M, Obrist WD, Amarnek WS *et al.* Differences in the distribution of gray and white matter in human cerebral hemispheres. *Science* 1980; **207**:1226–1228.
- Kohn MI, Tanna NK, Herman GT, Resnick SM, Mozley PD, Gur RE *et al.* Analysis of brain and cerebrospinal fluid volumes with MR imaging. Part I. Methods, reliability, and validation. *Radiology* 1991; **178**:115–122.
- Geschwind N, Levitsky W. Human brain: left-right asymmetries in temporal speech region. *Science* 1968; **161**:186–187.
- Tzourio N, Nkanga-Ngila B, Mazoyer B. Left planum temporale surface correlates with functional dominance during story listening. *Neuroreport* 1998; **9**:829–833.
- Amunts K, Jancke L, Mohlberg H, Steinmetz H, Zilles K. Interhemispheric asymmetry of the human motor cortex related to handedness and gender. *Neuropsychologia* 2000; **38**:304–312.
- Good CD, Johnsrude I, Ashburner J, Henson RN, Friston KJ, Frackowiak RS. Cerebral asymmetry and the effects of sex and handedness on brain structure: a voxel-based morphometric analysis of 465 normal adult human brains. *Neuroimage* 2001; **14**:685–700.
- Golestani N, Paus T, Zatorre RJ. Anatomical correlates of learning novel speech sounds. *Neuron* 2002; **35**:997–1010.
- Gur RC, Turetsky BI, Matsui M, Yan M, Bilker W, Hughett P *et al.* Sex differences in brain gray and white matter in healthy young adults: correlations with cognitive performance. *J Neurosci* 1999; **19**:4065–4072.
- Basser PJ, Mattiello J, Le Bihan DJ. MR diffusion tensor spectroscopy and imaging. *Biophys J* 1994; **66**:259–267.
- Klingberg T, Hedehus M, Temple E, Salz T, Gabrieli JD, Moseley ME *et al.* Microstructure of temporo-parietal white matter as a basis for reading ability: evidence from diffusion tensor magnetic resonance imaging. *Neuron* 2000; **25**:493–500.
- Conturo TE, Lori NF, Cull TS, Akbudak E, Snyder AZ, Shimony JS *et al.* Tracking neuronal fiber pathways in the living human brain. *Proc Natl Acad Sci USA* 1999; **96**:10422–10427.
- Wakana S, Jiang H, Nagae-Poetscher LM, van Zijl PC, Mori S. Fiber tract-based atlas of human white matter anatomy. *Radiology* 2004; **230**:77–87.
- Mori S, van Zijl PC. Fiber tracking: principles and strategies – a technical review. *NMR Biomed* 2002; **15**:468–480.
- Masutani Y, Aoki S, Abe O, Hayashi N, Otomo K. MR diffusion tensor imaging: recent advance and new techniques for diffusion tensor visualization. *Eur J Radiol* 2003; **46**:53–66.
- Anderson JM, Gilmore R, Roper S, Crosson B, Bauer RM, Nadeau S *et al.* Conduction aphasia and the arcuate fasciculus: a reexamination of the Wernicke–Geschwind model. *Brain Lang* 1999; **70**:1–12.
- Raczkowski D, Kalat JW, Nebes R. Reliability and validity of some handedness questionnaire items. *Neuropsychologia* 1974; **12**:43–47.
- Cao Y, Whalen S, Huang J, Berger KL, DeLano MC. Asymmetry of subinsular anisotropy by *in vivo* diffusion tensor imaging. *Hum Brain Mapp* 2003; **20**:82–90.
- Park HJ, Westin CF, Kubicki M, Maier SE, Niznikiewicz M, Baer A *et al.* White matter hemisphere asymmetries in healthy subjects and in schizophrenia: a diffusion tensor MRI study. *Neuroimage* 2004; **23**:213–223.
- Buchel C, Raedler T, Sommer M, Sach M, Weiller C, Koch MA. White matter asymmetry in the human brain: a diffusion tensor MRI study. *Cereb Cortex* 2004; **14**:945–951.
- Shaywitz BA, Shaywitz SE, Pugh KR, Constable RT, Skudlarski P, Fulbright RK *et al.* Sex differences in the functional organization of the brain for language. *Nature* 1995; **373**:607–609.
- Shaywitz SE, Shaywitz BA, Pugh KR, Fulbright RK, Constable RT, Mencl WE *et al.* Functional disruption in the organization of the brain for reading in dyslexia. *Proc Natl Acad Sci USA* 1998; **95**:2636–2641.
- Jancke L, Hanggi J, Steinmetz H. Morphological brain differences between adult stutterers and non-stutterers. *BMC Neurol* 2004; **4**:23.

Acknowledgements: This work was supported by NIH grants MH064045 and MH060722, and the Philips Medical Systems/RSNA Research Resident Grant.

AUTHOR QUERY FORM

**LIPPINCOTT
WILLIAMS AND WILKINS**

JOURNAL NAME **WNR**

4/6/05

ARTICLE NO: **3048**

QUERIES AND / OR REMARKS

Query No	Details Required	Authors Response
	No queries	