

The evolution of the arcuate fasciculus revealed with comparative DTI

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The arcuate fasciculus is a white-matter fiber tract that is involved in human language. Here we compared cortical connectivity in humans, chimpanzees and macaques (*Macaca mulatta*) and found a prominent temporal lobe projection of the human arcuate fasciculus that is much smaller or absent in nonhuman primates. This human specialization may be relevant to the evolution of language.

The arcuate fasciculus is a white-matter fiber tract that links lateral temporal cortex with frontal cortex via a dorsal projection that arches around the Sylvian fissure. Lesion studies indicate that this pathway is critically involved with human language¹. Gross dissections of the human brain revealed its general trajectory², but recent diffusion tensor imaging (DTI) studies have revealed its specific terminations. The temporal projection of the arcuate reaches the superior (STG), middle (MTG) and inferior (ITG) temporal gyri, whereas the frontal projection reaches the ventral premotor cortex (BA 6), pars opercularis (BA 44), pars triangularis (BA 45) and the middle frontal gyrus (BA 9)^{3,4}. The arcuate fasciculus of macaque monkeys has been explored using a different methodology, neuronal tracer injections. These studies show that the macaque arcuate links posterior STG with posterior dorsolateral prefrontal cortex⁵. Collectively, these findings suggest that there may be differences in the trajectory of the arcuate between humans and macaques. However, the arcuate has not yet been compared in humans and nonhuman primates using the same method. Moreover, the arcuate has not been explored in our closest living primate relative, the chimpanzee, and, without these comparison data, it is not possible to make inferences about human brain specializations or human brain evolution. The recent advent of DTI, which can track white-matter pathways noninvasively, makes it possible to compare patterns of connectivity in humans and

nonhuman species. Here, we use DTI to compare the organization of the arcuate fasciculus in humans, chimpanzees and macaques.

We acquired DTI brain scans from ten live human subjects, three postmortem chimpanzee brains and two postmortem macaque brains (see **Supplementary Table 1** and **Supplementary Methods** online). All protocols were approved by the Emory University Institutional Animal Care and Use Committee and Institutional Review Board, and written informed consent was obtained from all human subjects. Postmortem scanning makes it possible to scan longer and achieve higher spatial resolution in the smaller nonhuman brains than would be possible with *in vivo* scanning. *In vivo* scans obtained from one chimpanzee and one macaque yielded results for the arcuate fasciculus that were very similar to those obtained in the postmortem scans, confirming that any interspecies differences were not a result of brain fixation (**Supplementary Fig. 1** and **Supplementary Methods** online). Moreover, when we compared the organization of the corticospinal tract and cingulum bundle, two pathways for which we have no a priori grounds to expect strong species differences, we found them to be very similar in the *in vivo* human and postmortem nonhuman primate scans (**Supplementary Fig. 2** and **Supplementary Methods** online).

Principal diffusion-direction color maps in the region of the arcuate fasciculus revealed noteworthy differences between the species (**Fig. 1**). In humans, the dorsal portion of the arcuate, which traveled in an anterior-posterior direction, as indicated by its green color, transitioned into blue where the pathway descended into the temporal lobe. In chimpanzees, a small region of red (mediolaterally directed fibers) interrupted the transition from green to blue in the hook of the arcuate. In macaques, the red area is considerably expanded and the color map in the region of the arcuate bore little resemblance to human or chimpanzee color maps. Thus, only in the human brain was a continuous, uninterrupted arcuate pathway evident in the color map of the principal diffusion direction. It was possible, however, that in

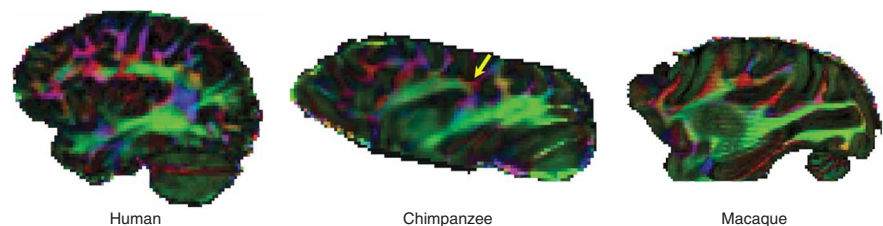


Figure 1 Color maps of principal diffusion direction in one *in vivo* human, one postmortem chimpanzee and one postmortem rhesus macaque brain. Yellow arrow points to red, mediolaterally oriented fibers in chimpanzee brain.

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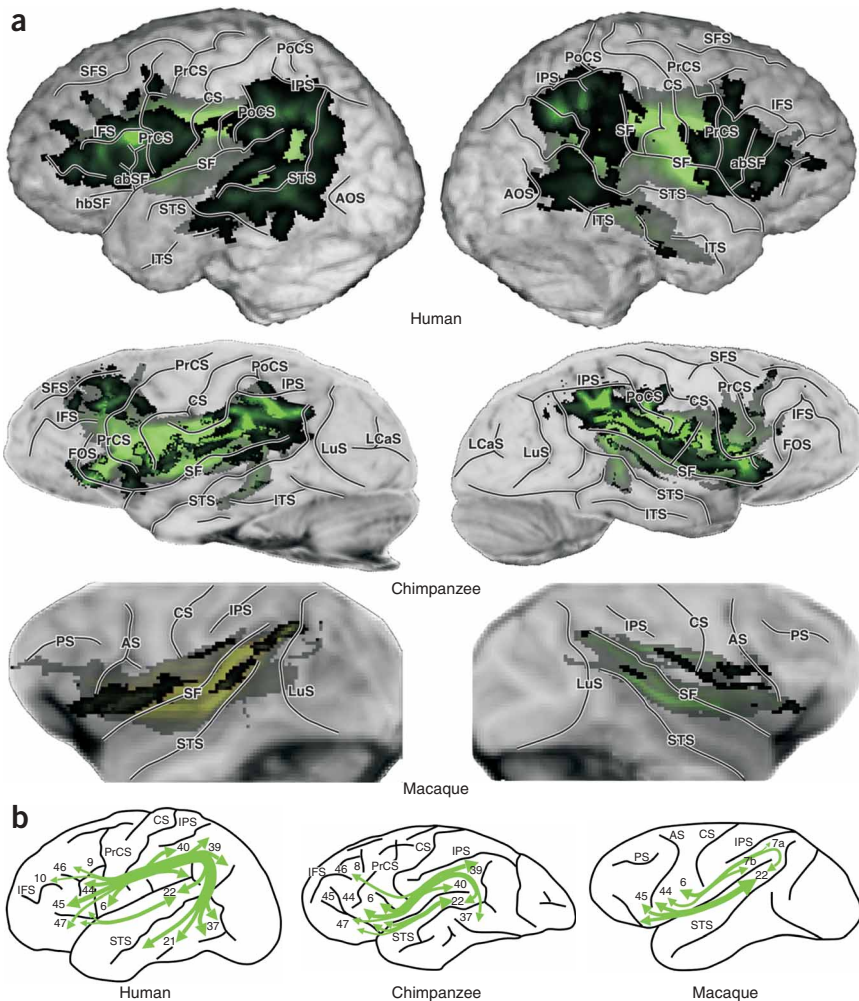


Figure 2 Three-dimensional tractography results. **(a)** Average tractography results for humans, chimpanzees and macaques, showing left and right hemisphere results. **(b)** Schematic summary of results shown in **a**. Center of gravity of human MTG projections at $x = \pm 48$ are at Montreal Neurological Institute coordinates, $x = -48$, $y = -42$, $z = -3$ and $x = 48$, $y = -36$, $z = -7$. abSF, ascending branch of the Sylvian fissure; AOS, anterior occipital sulcus; AS, arcuate sulcus; CS, central sulcus; FOS, fronto-orbital sulcus; hbSF, horizontal branch of the Sylvian fissure; IFS, inferior frontal sulcus; IPS, intraparietal sulcus; ITS, inferior temporal sulcus; LCaS, lateral calcarine sulcus; LuS, lunate sulcus; PoCS, postcentral sulcus; PrCS, precentral sulcus; PS, principal sulcus; SF, Sylvian fissure; SFS, superior frontal sulcus; STS, superior temporal sulcus.

the inferolateral margin of the frontal lobe (area 6), including the extreme ventral aspects of areas 44 and 45 in the arcuate sulcus, with the strongest terminations being in area 45 (Fig. 2a,b and Supplementary Fig. 1). These results are consistent with prior tracer⁵ and DTI⁷ studies in macaques (Fig. 3a).

Tracking in chimpanzees revealed that, unlike macaques, the pathway running dorsal to the insula was stronger than that of the extreme capsule (Fig. 3a). Cortical terminations were more widespread than in macaques, involving prominently the inferior parietal lobule, including both the supramarginal gyrus (area 40) and the angular gyrus (area 39), as well as dorsolateral prefrontal and dorsal premotor cortex (Fig. 2a,b and Supplementary Fig. 1). In chimpanzees, this

dorsal pathway was dominated by connections with the inferior parietal lobe (supramarginal gyrus and angular gyrus).

Tracking in humans, as in chimpanzees, revealed that the dorsal pathway was dominant to the extreme capsule pathway (Fig. 3a). The cortical terminations of humans also differed from chimpanzees and macaques, with humans having much stronger terminations posteriorly, in the MTG and ITG, as well as anteriorly, in pars opercularis (BA 44), pars triangularis (BA 45), pars orbitalis (BA 47) and surrounding regions (Fig. 2a,b and Supplementary Fig. 1). Terminations in the MTG and ITG were found in 10 of 10 human brains, 1 of 4 chimpanzee brains and 0 of 3 macaque brains ($\chi^2 = 56.5$, degrees of freedom = 2, $P < 0.0001$), and human terminations were more extensive than those of the lone chimpanzee subject who also had them (Supplementary Fig. 1). Connectivity with the MTG was more widespread and of higher probability in the left than in the right hemisphere, consistent with functional imaging evidence that lexical-semantic (word-meaning) processing is lateralized to left MTG and angular gyrus⁸, and with studies reporting leftward asymmetries in the human arcuate fasciculus^{3,4}. In humans, tracts extending into the temporal lobe via the arcuate fasciculus made a much greater contribution to the dorsal pathway (Fig. 3b) than they did in chimpanzees. Substantial evidence indicates that the MTG is involved in lexical-semantic processing⁸ and that pars triangularis and pars orbitalis are involved in syntactic processes of sentence comprehension⁹. To explore whether these two regions were specifically connected with one

chimpanzees, at least, the arcuate actually did pass into the temporal lobe, but that standard tractography algorithms, which consider only the principal diffusion direction, cannot follow it through a region where it intermingles with a different, mediolaterally oriented pathway. For this reason, we used a newly developed algorithm designed to track through crossing fibers by also considering the secondary diffusion direction⁶.

We used this technique to track the arcuate fasciculus, along with two additional pathways that convey fibers between frontal and parietal-temporal cortex, the superior longitudinal fasciculus and the extreme capsule. These pathways can be clearly identified in a coronal section through the color map at the level of the precentral sulcus (Supplementary Fig. 3 online). In all three species, we tracked between a coronal region of interest (ROI) that encompassed these three pathways and an ROI in the white matter underlying the STG, MTG and ITG, as well as the inferior parietal lobule (Supplementary Fig. 3 and Supplementary Methods). Note that the surface anatomy of the macaque temporal lobe differs from those of humans and chimpanzees: the less-convoluted macaques lack an inferior temporal sulcus, so that there is no distinction between MTG and ITG.

Tracking results in macaques revealed that the pathway of highest probability ran in the vicinity of the extreme capsule deep to the insula, with weaker pathways running both dorsal and lateral to the insula. Posteriorly, cortical terminations were observed in posterior STG (area 22) and anterior inferior parietal cortex (area 7b). Anteriorly, terminations were found in the frontal operculum, insular cortex and

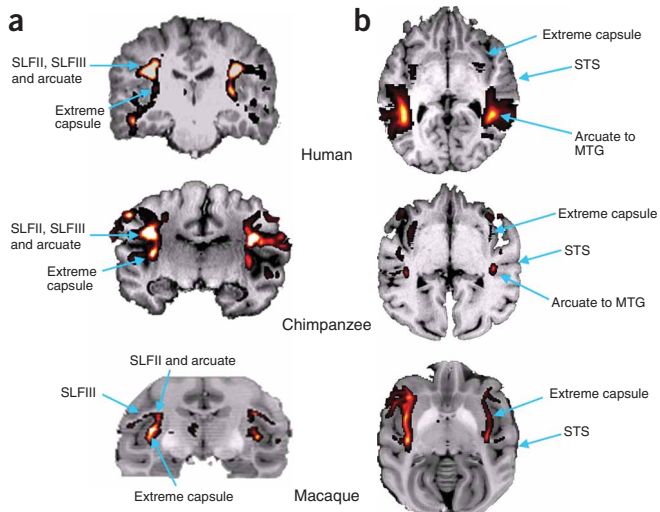


Figure 3 Two-dimensional tractography results. (a,b) Coronal (a) and axial (b) sections from an individual human, chimpanzee and macaque, illustrating the relative strength of the dorsal and ventral pathways. SLFII and SLFIII, superior longitudinal fasciculus II and III.

another, we quantified the probability of connectivity between the region of the MTG cortex where terminations were found and each of two anatomically defined ROIs: one spanning pars opercularis (BA 44) and the other including both pars triangularis (BA 45) and pars orbitalis (BA 47). In both hemispheres, MTG had a higher probability of connectivity with pars triangularis and pars orbitalis than with pars opercularis (**Supplementary Fig. 4** online). This raises the possibility that the expanded pathway in humans supports the transmission of word-meaning information stored in the MTG and angular gyrus to pars triangularis and orbitalis for both sentence comprehension and sentence construction during spontaneous speech.

In conclusion, our results indicate that the organization and cortical terminations of the arcuate fasciculus were strongly modified in human evolution. Notably, in humans, but not chimps or macaques, frontal cortex of the left hemisphere was strongly connected via the arcuate fasciculus with the left MTG and ITG, ventral and anterior to the cortex usually included in Wernicke's area (**Fig. 2b**). In macaques, this region consists mainly of extrastriate visual cortex, whereas in humans it represents word meaning¹⁰. We suggest that the MTG and ITG cortex enlarged disproportionately in the human lineage, following the divergence of the human and chimpanzee lineages, possibly with the addition of new cortical fields, and that in humans, new connections were established between this region and Broca's area, linking regions that are involved in lexical-semantic and syntactic processing in modern humans. This would account for the apparent posterior

displacement of extrastriate visual areas in humans compared with macaques^{10,11} and is consistent with evidence that both frontal^{12,13} and temporal-lobe white-matter volume increased disproportionately in human evolution¹⁰. Our results also suggest that the evolution of language entailed modifications of cortical areas and pathways that mediate specific linguistic functions and was not an incidental byproduct of selection for general brain-size enlargement¹⁴. This does not preclude the possibility that the modified pathways mediate functions in addition to language, such as tool use¹⁵, although the correspondence between the structures modified in human evolution identified in this study and structures known to be involved in language function is notable.

Note: Supplementary information is available on the Nature Neuroscience website.

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AUTHOR CONTRIBUTIONS

J.K.R. designed the study, acquired the nonhuman data, supervised analyses and wrote the paper. M.F.G. analyzed the data. T.M.P. acquired the nonhuman brains, assisted with data analysis and presentation, and wrote the paper. X.M., T.Z. and X.H. assisted with nonhuman primate protocol development, and T.E.J.B. and Oxford colleagues acquired the human data. T.E.J.B. oversaw the data-analysis strategy with the exception of the *in vivo* chimpanzee and macaque data presented in the supplementary information.

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