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Human middle longitudinal fascicle: variations in patterns of anatomical connections

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Abstract

Based on high-resolution diffusion tensor magnetic resonance imaging (DTI) tractographic analyses in thirty-nine healthy adult subjects we derived patterns of connections and measures of volume and biophysical parameters, such as fractional anisotropy (FA) for the human middle longitudinal fascicle (MdLF). Compared to previous studies, we found that the cortical connections of the MdLF in humans appear to go beyond the superior temporal (STG) and angular (AG) gyri, extending to the temporal pole (TP), superior parietal lobule (SPL), supramarginal gyrus, precuneus and the occipital lobe (including the cuneus and lateral occipital areas). Importantly, the MdLF showed a striking lateralized pattern with predominant connections between the TP, STG and AG on the left and TP, STG and SPL on the right hemisphere. In light of the results of the present study, and of the known functional role of the cortical areas interconnected by the MdLF, we suggested that this fiber pathway might be related to language, high order auditory association, visuospatial and attention functions.

Keywords

Diffusion tensor tractography; Middle longitudinal fascicle; Angular gyrus; Superior parietal lobule; Superior temporal gyrus; Language

Introduction

The anatomy of long association corticocortical fiber pathways in the human brain has been demonstrated in recent years by several investigators using imaging techniques such as diffusion tensor magnetic resonance imaging (DTI) (see e.g., Catani et al. 2002; Makris et al. 1997; Mori 2002). These studies have corroborated and extended previous classical anatomical descriptions of these fiber tracts (Burdach 1822; Dejerine 1895; Ludwig and Klingler 1956). One of the most prominent postrolandic association fiber bundles, the middle longitudinal fascicle (MdLF), is located within the superior temporal gyrus (STG) coursing from the temporal pole to the caudal end of STG and extends further dorsally and caudally inside the inferior parietal lobule (IPL) (angular gyrus, AG) (Makris et al. 2009). Although prominent in size and location, the MdLF had not been noted by pioneers of human neuroanatomy and its existence has been demonstrated in the human brain only recently (Makris et al. 2009). In humans, the MdLF is distinct from other long association fiber tracts connecting the frontal lobe with the parietal or temporal lobes such as the superior longitudinal fascicles II and III (SLF II and SLF III) or the arcuate fascicle (AF), respectively, and the extreme capsule (EmC) (Makris and Pandya 2009; Makris et al. 2009).

The MdLF was originally demonstrated in the rhesus monkey by Seltzer and Pandya (1984), as a distinct fiber tract originating from the inferior parietal lobule and coursing rostrally within the white matter of the STG terminating in the cortical areas along the upper bank and depth of the superior temporal sulcus (areas TPO, PGA and IPa). The use of autoradiography in the experimental animal allowed the accurate delineation of MdLF's connections, namely its precise architectonic origins and terminations (Seltzer and Pandya 1984). Recently, this fiber pathway has also been demonstrated by diffusion spectrum imaging in the monkey (Schmahmann et al. 2007).

In humans, gross dissection and fixation techniques (Dejerine 1895) as well as myelin staining or fiber dissection (Ludwig and Klingler 1956), and currently DTI (Basser et al. 1994; Basser and Pierpaoli 1996), enable us to characterize several features of a long association fiber pathway such as its morphology, trajectory, location and general connections. Yet, the techniques do not allow the precise delineation of the architectonic origins and terminations (Makris et al. 2002b; Schmahmann and Pandya 2006). Therefore, due to these methodological limitations, the precise and complete connections of MdLF have not been demonstrated with certainty in humans and extrapolation of anatomical information from the experimental animal to humans has been proven to be useful (Makris et al. 2002b; Schmahmann and Pandya 2006). However, as has been shown recently there exist considerable anatomical differences between humans and non-human primates with respect to different association fiber pathways (Makris et al. 2005; Rilling et al. 2008). The existence of such a difference may be particularly applicable to the MdLF, which may be related to language function, thus it seems reasonable to assume that the connections of MdLF in humans may differ somewhat from those in the monkey. Nevertheless, DTI tractography has been shown to be a useful tool for discerning different fiber tracts (Catani et al. 2002; Lori et al. 2002; Mori et al. 1999) and has enabled us to differentiate the MdLF from other long association fiber pathways such as the extreme capsule (EmC) or the inferior longitudinal fascicle (ILF), and from the AF in particular, whose trajectories are adjacent to each other within the temporal and parietal lobes (Makris et al. 2009). Moreover, the use of DTI can yield clinically relevant information regarding size and biophysical characteristics of fiber tracts such as the MdLF.

We hypothesized that the connections of MdLF would be more extensive in the human than just between the STG and AG as has been demonstrated in humans and monkeys to-date. We based this hypothesis on previously published data in humans (Makris et al. 2009;

Turken and Dronkers 2011), the known anatomy of MdLF in the rhesus monkey (Seltzer and Pandya 1984) and the known significant modifications that cortical areas and fiber pathways related to language have undergone during evolution (Rilling et al. 2008). Thus, in thirty-nine (39) healthy human subjects (i.e., in a total of seventy-eight (78) middle longitudinal fascicles) we investigated bilaterally the anatomical connections of MdLF within the temporal, parietal and occipital regions, in an attempt to detail further the anatomical connectivity of this fiber pathway. Furthermore, we mapped the MdLF of all subjects in the MNI152 standard stereotactic space (Evans et al. 1993), to provide a more informed chartographic representation of the patterns and variability of its connections in the normal population. Finally, we generated a database of biophysical parameters for the MdLF, such as fractional anisotropy (FA) (Basser 2004), axial diffusivity (AD) (Song et al. 2003), radial diffusivity (RD) (Song et al. 2003; Song et al. 2002), volume, length and their left-right asymmetries.

Methods

We used magnetic DTI-based tractography in thirty-nine human subjects to achieve three goals. First, we delineated the trajectory and anatomical connections of MdLF within the temporal, parietal and occipital regions. We also derived the Talairach coordinates of the center of mass for each individual tractographic “seed” region of MdLF. Second, we mapped the MdLF of all subjects as well as the most frequently observed patterns in our population in the MNI152 standard space. Third, we generated a database of biophysical parameters, such as FA, AD, RD, volume, length and symmetry in this population of healthy human subjects.

Subjects

Thirty-nine healthy subjects, thirty-five males and four females, participated in the study. All subjects were 17 to 55 years old (34.8 on average), right-handed, average IQ = 113, with no diagnosed neurological disorder, and no lifetime history of alcohol or other drug dependence. They were recruited through newspaper advertisements as part of a larger study, and were ascertained to have no Axis I disorder using the SCID I for Non-Patients (First et al. 1997). This study was approved by the local IRB at both the VA Boston Healthcare System, Brockton, MA campus and Brigham and Women's Hospital. Written informed consent was obtained from all subjects prior to study participation.

MRI procedures

All subjects were scanned on a 3T GE Echospeed system (General Electric Medical Systems, Milwaukee, WI). Scans included a T1-weighted, a T2-weighted and an echo planar imaging (EPI) DTI pulse sequence. The T1-weighted sequence consisted of the following parameters: TR = 7.4 ms, TE = 3 ms, TI = 600, 10° flip angle, 25.6 cm² field of view, matrix = 256 × 256. The voxel dimensions were 1 × 1 × 1 mm. The T2-weighted acquisition (namely, eXtended Echo Train Acquisition) produced a series of contiguous images using TR = 2500 ms, TE = 80 ms, 25.6 cm² field of view, with voxel dimensions 1 × 1 × 1 mm. Finally, for the DTI, a double echo sequence (Alexander et al. 1997; Heid 2000) with an 8 Channel coil and ASSET (Array Spatial Sensitivity Encoding Techniques, GE) with a SENSE-factor (speed-up) of 2 was used to reduce eddy-current and EPI spatial related distortions. A product GE sequence was modified to accommodate for higher spatial resolution (Spatial-Spectral Pulse was replaced by Fat- Sat suppression pulse, echo spacing was also decreased by 15% to accommodate for more slices per TR). Fifty-one (51) noncolinear diffusion directions with b = 900 and eight baseline scans with b = 0 were acquired. Eighty-five (85) axial slices parallel to the AC-PC (anterior commissure-posterior commissure) line spanning the entire brain (no gap) were collected for each subject. Scan

parameters were as follows: TR = 17000 ms, TE = 78 ms, FOV = 24 cm, 144×144 encoding steps with slice thickness = 1.7 mm, producing isotropic $1.7 \times 1.7 \times 1.7$ mm voxels. Total scanning time for the DTI sequence was 17 minutes. Diffusion data were prepared by removing motion and eddy current artifacts from the raw data using software based on FSL (<http://www.fmrib.ox.ac.uk/fsl>). Noise filtering was done using a one-step and a recursive LMMSE estimator for signal estimation and noise removal assuming a Rician noise model (Aja-Fernandez et al. 2008). After reconstruction, diffusion-weighted images were transferred to a LINUX workstation, on which diffusion tensors were estimated in slicer3D software, and then FA, AD and RD were calculated for each voxel.

Tractographic delineation of MdLF

Diffusion tractography was performed in 3D-slicer (v2.7, www.slicer.org). Tractography allows the delineation of the trajectory, the differentiation between adjacent fiber tracts, the mapping of their topographic anatomy and their quantification (Catani et al. 2002; Makris et al. 2005; Makris et al. 2009; Mori et al. 1999). The method for tractography has been described in several of our previous publications (Fitzsimmons et al. 2009; Oh et al. 2009; Rosenberger et al. 2008). Briefly, an eigenvector tracking algorithm based on the fourth order Runge-Kutta method for tracking axonal fibers was implemented. Since this method is highly dependent on the major eigenvector, it cannot continue fiber tracking in regions where fibers cross, where the anisotropy is low, or orientation is not continuous with the previous direction. Therefore, we used a regularization scheme, where a small bias towards the previous tracking direction to the current tensor was added. Fiber tracks were visualized using the stream tube method.

Sampling of the “seed” and fiber tract reconstruction—To delineate the MdLF, three “seed” ROIs that included white matter of the STG were drawn on the FA map following a variation of the description in Makris et al. (2009). By selecting voxels only within the white matter of STG, we assured that all voxels pertaining to the “stem” portion (Makris et al. 1997) of MdLF in STG were sampled. For the STG ROIs, we first identified a coronal slice that unambiguously depicted the frontotemporal transition on the FA map (slice1 in Figure 1). The first ROI was then drawn on a coronal slice, six slices (i.e., 10.32 mm) posterior to the frontotemporal transition (slice1 in Figure 1). The second ROI was six coronal slices posterior to the first ROI (slice2 in Figure 1), and the third one was six coronal slices posterior to the second (slice3 in Figure 1). In these three coronal slices we sampled all white matter voxels within the STG. Tracts were seeded in the STG ROIs, and all fibers traveling through the ROIs were included in the analysis (Figure 1). Based on our previous experience (Makris et al. 2009) and the Talairach coordinate system (Talairach and Tournoux 1988), in which the STG extends for 55 mm in the Y-axis, i.e., the anteriorposterior dimension, the positioning of the three ROIs was designed to sample the fibers of MdLF by seeding within the anterior half of the white matter of this gyrus. Interpolated Streamline deterministic algorithm was then used in Slicer3D using FA threshold of 0.15 and tract seeds were placed randomly at $1 \times 1 \times 1$ mm grid on the FA maps (Jones et al. 2006). Finally, the FA, Radial $(\lambda_2 + \lambda_3) / 2$ and Axial (λ_1) Diffusivity were calculated at every voxel along the MdLF, and averaged along each tract for each subject. The Talairach coordinates of the center of mass of the “seed” for the MdLF were calculated in every individual in each coronal slice in which the seed was sampled.

Reliability and differentiation of MdLF from other fiber tracts—All manual processes were conducted by a trained researcher (MGP). To assess inter-rater reliability, two raters evaluated five randomly selected cases (i.e., ten middle longitudinal fascicles) (NM and MGP); intra-rater reliability was also assessed for one rater (MGP) on the same five cases (i.e., ten hemispheres). To confirm our results unequivocally, we also

differentiated the MdLF from the arcuate fascicle (AF), which courses adjacent to MdLF in a considerable part of its trajectory within the IPL and posterior STG. Furthermore, for completion, we also traced all other long association fiber pathways within the hemisphere, specifically, the SLF II and SLF III (Makris et al. 2005), EmC/IFOF (Makris and Pandya 2009), ILF (Makris and Pandya 2009), superior occipitofrontal fascicle (Makris et al. 2007), uncinate fascicle (UF) (Makris and Pandya 2009) and CB (Makris et al. 2002a) following procedures described by our group (Makris et al. 2005; Makris et al. 2002a; Makris et al. 2009; Makris et al. 2007). To this end, in these five cases, all these long association fiber bundles were delineated tractographically comprehensively in ten hemispheres by one of the raters (NM) (Makris et al. 2005; Makris and Pandya 2009; Makris et al. 2002a; Makris et al. 2009; Makris et al. 2007).

Corticocortical connections of MdLF—To elucidate the corticocortical connections of MdLF, the reconstruction of the cortex is necessary (Makris et al. 2009). To derive cortical regions of interest (ROIs), we applied, on the MNI152 standard dataset, cortical segmentation and parcellation morphometric techniques used at the Center for Morphometric Analysis at Massachusetts General Hospital as described in previous publications of our group (Caviness et al. 1996; Filipek et al. 1994; Rademacher et al. 1992). To test our hypothesis that MdLF in humans would have more extensive connections than has been demonstrated in non-human primates and currently in humans, we investigated superior temporal, lateral and medial parietal and occipital regions in the cerebral cortex, more specifically, the temporal pole (TP, BA 38), superior temporal gyrus (STG, principally BA 22 and 42), angular gyrus (AG, BA 39), supramarginal gyrus (SMG, BA 40), superior parietal lobule (SPL, BA 7), precuneus (PCN, BA 7), temporooccipital region (T-O, caudal BA 21 and BA 37) and the occipital lobe (OCC, BA 18 and 19). It should be noted that associating cortical regions to Brodmann's areas was done herein only as a scheme of anatomical orientation, given that identification of cytoarchitectonic areas has not yet been demonstrated with DTI. Next, we annotated the connections of MdLF with the hypothesized cortical ROIs for each subject in a table. Finally, based on that table we derived all possible connectional patterns of MdLF, which we rank-ordered based on the frequency, namely the percentage, of their occurrence.

Mapping the average MdLF of all subjects in a common space

We mapped the MdLF in the MNI152 standard space by aligning and merging the virtual tracts of all subjects to visualize them in the same coordinate space. A “virtual tract” is a common term used currently in computational anatomy referring to the computerized reconstruction of axons as represented by DTI-based tractography. The FA images of every subject were linearly aligned to the FMRIB58_FA template in MNI152 coordinates with FSL FLIRT and the identical registration was applied to the virtual tracts of every individual. Subsequently, the aligned virtual tracts of all subjects were merged together using TrackVis (Wang et al. 2007).

Quantitative Analyses

Measurements of volume, length, mean FA, mean AD and mean RD of the left and the right MdLF were obtained in 39 healthy human subjects (78 middle longitudinal fascicles). FA, AD and RD are biophysical parameters of DTI that may relate to fiber tract coherence and integrity (Basser 2004; Song et al. 2003; Song et al. 2002). *Symmetry Index (SI)* between left and right MdLF for volume, mean FA, mean AD and mean RD were calculated for each individual and for all subjects as well. Symmetry Index is defined as follows: $SI = (Left - Right) / 0.5 (Left + Right)$ (Galaburda et al. 1987).

Results

Delineation of MdLF and its connections

We were able to delineate the MdLF in thirty-nine human subjects bilaterally (i.e., 78 middle longitudinal fascicles) (Figure 2A). Inter- and intra-rater reliability for FA values and volume was high. Specifically, with respect to FA, intraclass correlation coefficients (Cronbach's alpha) achieved for inter-rater reliability were .99 for the left FA and .96 for the right MdLF FA. Likewise for intra-rater reliability, Cronbach's alpha was .96 for the left FA and .96 for the right MdLF FA. With respect to volume, intraclass correlation coefficients (Cronbach's alpha) achieved for inter-rater reliability was .87 on the left and .97 on the right MdLF. Likewise for intra-rater reliability, Cronbach's alpha was .89 on the left and .76 on the right MdLF. We also demonstrated differentiation of MdLF from other fiber tracts in Figure 2B. In each subject we examined the connections of MdLF within the temporal, parietal and occipital lobes and annotated them on the right and left hemisphere as shown in Table 1a. In general, the MdLF connected with the temporal pole (TP), superior temporal gyrus (STG), angular gyrus (AG), supramarginal gyrus (SMG), superior parietal lobule (SPL), precuneus (PCN), temporo-occipital region (T-O) and the occipital lobe (OCC). The most frequent connections were with the STG (100%) (which was expected, given the location of the tractographic "seed" within the STG white matter) and dorsal region of the temporal pole (90%), angular gyrus (67%), superior parietal lobule (41%), precuneus (27%), supramarginal gyrus (10%), occipital lobe (14%) (including the cuneus and lateral occipital regions) and temporo-occipital region (8%) (Table 1a). The anatomical connectivity of MdLF presented high variability and several patterns, with pronounced differences between the two hemispheres. Specifically, there were observed several combinations of MdLF connecting subsets of the eight cortical ROIs, the most frequently observed of which are reported in Table 1b. The most common pattern in the left hemisphere showed MdLF connecting TP, STG and AG, which was present in 31% of subjects, i.e., in 12 of the 39 left hemispheres. In the right hemisphere instead, the most frequently observed pattern showed MdLF connecting with TP, STG and SPL, which was present in 18% of subjects, i.e., in 7 of the 39 right hemispheres. This is illustrated in the left and right hemispheres of an individual subject in Figure 3.

Mapping of MdLF in a common space

We mapped seventy-eight MdLFs (39 on each hemisphere) on the MNI152 standard space satisfactorily. The results of virtual fibers of all subjects merged together in the MNI152 standard coordinate space are shown in Figure 4. Furthermore, the connections of these virtual fibers with different cortical regions are illustrated in Figure 5. We also demonstrated the three most common patterns observed on the left and right MdLF in Figure 6. The most common pattern in the left hemisphere showed MdLF connecting TP, STG and AG, which was present in 31% of subjects, i.e., in 12 of the 39 left hemispheres (6Ai-iv). This pattern was also present in the right hemisphere but only in 10% of the subjects, i.e., in 4 of the 39 right hemispheres (Figure 6Bviii-x). The most common pattern observed in the right hemisphere was MdLF connecting TP, STG and SPL, which occurred in 18% of instances on the right, i.e., in 7 of the 39 right hemispheres (Figure and 6Bi-iv) and 13% on the left hemisphere, i.e., in 5 of the 39 left hemispheres (Figure 6Av-vii). The third most frequently observed pattern of MdLF in the left hemisphere showed MdLF connecting TP, STG, SMG and AG (8%, i.e., in 3 of the 39 left hemispheres) (Figure 6Aviii-x). In the right hemisphere, another frequently observed pattern (10%, i.e., 4 of 39 right hemispheres) portrayed MdLF connecting TP, STG, AG and SPL (Figure 6Bv-vii).

The Talairach coordinates of the center of mass of the "seed" for the MdLF in 39 individuals were calculated and represented in Figure 7. Specifically, the three "seed" ROIs were

located consistently within the anterior half of STG in all subjects of our sample. Talairach coordinates for the anteriorposterior dimension represented in the Y-axis ranged from -8.3 mm to -24.6 mm in the right and from -9.7 mm to -26.2 in the left.

Quantitative results

Tract volumes, length, mean FA, mean AD, and mean RD of the left and right MdLF in 39 healthy human subjects are shown in Table 2. The mean volume of MdLF was 4.06 cm^3 on the left, and 4.19 cm^3 on the right, mean length was 17 cm on the left and 16.6 cm on the right, mean FA was .389 on the left and .395 on the right. Whereas, the mean AD of MdLF was 0.125 on the left, and 0.125 on the right, and mean RD 0.067 on the left, and 0.067 on the right.

Analysis of symmetry—Symmetry Index (SI) between left and right MdLF for volumes, length, mean FA mean AD and mean RD is reported for each individual in Table 2. None of those measures showed significant left-right differences in independent sample t-tests.

Discussion

In this study we analyzed seventy-eight middle longitudinal fascicles in thirty-nine healthy human subjects using DTI tractography. We were able to delineate MdLF within the superior temporal gyrus, inferior and superior parietal lobules and occipital lobe thus elucidating further its anatomical connectivity. Importantly, our results revealed an apparent lateralization and distinct patterns of MdLF connections in the cerebral hemispheres emphasizing the high degree of variability of this fiber tract in humans. Furthermore, we created the average map of MdLF in the MNI152 standard coordinate space. We also initiated the creation of a normative database and investigated right-left asymmetry of volume, length and biophysical parameters of this corticocortical long association fiber pathway in humans.

To our knowledge there are only a few published studies involving MdLF in humans (De Witt Hamer et al. 2011; Makris and Pandya 2009; Makris et al. 2009; Turken and Dronkers 2011). Nevertheless, this fiber tract has been already a topic of debate in terms of its structure and functional role in humans. So far, the MdLF has been considered as a long association fiber pathway connecting the superior temporal gyrus with the inferior parietal lobule (angular gyrus) in the human brain (Makris et al. 2009). These observations were in agreement with similar findings in the rhesus monkey (Seltzer and Pandya 1984). However, although extrapolating connectional information from the monkey to the human brain has been proven very valuable in guiding the discovery of novel connections of pathways such as the MdLF (Makris et al. 2009), relevant functional differences between the two species indicate that structural differences should be expected as well. This notion is particularly pertinent for the MdLF, which may be related to language function (Makris et al. 2009; Turken and Dronkers 2011). This has been shown recently with other association fiber tracts as well, such as the SLF I, SLF II and SLF III, which compared to the monkey data, “in the human extend more posteriorly within the dorsal parietal regions and parieto-occipital border zones. These fiber fascicles also extend more anteriorly within the frontal association areas. This may due to the fact that the parietal and frontal association regions are considerably expanded in the human” (Makris et al. 2005; p.863). Likewise, as Rilling et al. (2008) recently demonstrated for the arcuate fascicle, the organization and cortical terminations of this long association corticocortical fiber pathway were “strongly modified in human evolution.”

Connections of MdLF

The results of this study showed that MdLF connects with cortical areas in the temporal, parietal and occipital lobes, in addition to its known connections with STG and angular gyrus, as we have originally hypothesized and that these connections are lateralized. Specifically, we demonstrated using DTI-based tractography that in the 78 MdLFs studied herein, this fiber tract has its strongest connections with the dorsal region of the temporal pole, superior temporal gyrus, angular gyrus and superior parietal lobule. These connections have been shown to be bidirectional in monkeys (Petrides and Pandya 2002). This large group of MdLF connections in the human cerebrum may be due to the fact that the cortical association areas are considerably expanded in the human cerebrum. Moreover, these novel findings may reflect a distinctive functional role of MdLF in terms of its temporal, parietal and occipital cortical affiliations. Furthermore, we observed considerable variability in MdLF connections bilaterally, which may represent actual inter-individual differences in connections of the STG mainly with the inferior and superior parietal lobules. This may be explained by the fact that inter-individual variability in cytoarchitecture and cortical morphology is also very pronounced in these association areas (Ono et al. 1990; Rademacher et al. 1993; Rademacher et al. 1992; Sanides 1962). Thus the MdLF by virtue of connecting these cortical regions may reflect their degree of variation as well. Although beyond the scope of this study, it would be relevant knowing if this variability is systematic or random and thus understand how different patterns may be related to inheritance and what would be their adaptive significance. It should also be pointed out that given the limitations of DTI tractography, these observations should be taken into consideration with caution. The latter is particularly applicable for less frequently observed connections involving the supramarginal gyrus and occipital lobe.

Laterality of MdLF connections—Based on our findings the MdLF is lateralized in the human brain in terms of its connections. In the left hemisphere the connection of the superior temporal regions (i.e., dorsal TP and STG) with the inferior parietal lobule, in particular the angular gyrus (AG) seems to be predominant. By contrast, on the right the prevalent connection appears to be between the superior temporal regions (dorsal TP and STG) and the superior parietal lobule (SPL). As shown in Table 1b, we observed several different patterns of connections in both hemispheres. Although structural asymmetries in cortical areas such as the planum temporale (Geschwind and Levitsky 1968) have been known for a long time, this notion remains obsolete for connectional patterns of fiber pathways. Differences in size or biophysical parameters of fiber tracts between the two hemispheres are indicative of structural and functional laterality (Nucifora et al. 2005; Rodrigo et al. 2007; Thiebaut de Schotten et al. 2011b) and have supported known anatomical and functional asymmetries in the human brain. The notion of asymmetry in pattern of connections, however, is different and may represent something more profound, more organizational. Cortical areas associated with language function are poorly represented in the non-human primate. The angular gyrus (BA 39) and supramarginal gyrus (BA 40) seem to be the latest to myelinate in the human cerebrum (Flechsigs 1901), which bears credence to the thought that these two cortical regions may have developed as novel neocortical areas (Eccles 1989). The fact that MdLF is asymmetrical in nature in the left and right hemispheres with respect to its connections should be considered further in the context of cerebral systems organization, evolution and lateralization of function in humans.

Functional role of MdLF

Given its location within the superior temporal gyrus and the inferior parietal lobule, it has been suggested that MdLF plays a role in language (Makris and Pandya 2009; Makris et al. 2009) and attention functions (Makris et al. 2009). However, more recent observations using DTI have opened a debate regarding its structure and function (De Witt Hamer et al. 2011;

Turken and Dronkers 2011). Specifically, De Witt Hamer et al. (2011), based on intraoperative brain electrostimulation observations using a picture naming task as well as pre- and post-operative behavioral testing of language function questioned the existence of MdLF and its functional role with respect to language. By contrast, Turken and Dronkers studying structural and functional connectivity of brain regions related to auditory sentence comprehension such as the anterior part of STG and the angular gyrus, suggested that MdLF is part of the language comprehension network (Turken and Dronkers 2011). In the light of the results of the present study, based on the known functional role of the cortical areas that are interconnected by the MdLF, some general comments regarding the putative functional role of this fiber system related to the language, high order auditory association, integrative audiovisual, visuospatial and attention functions can be made.

Possible functional role of MdLF in language—Recently, a model of speech processing has been proposed by (Hickok and Poeppel 2000), attempting to clarify the functional anatomy of language based on considerations of task effects when mapping speech-related processing systems (Hickok 2001; Hickok and Poeppel 2007). According to this model, a ventral temporo-frontal stream is responsible for auditory comprehension by processing speech signals and mapping speech input into meaning, whereas a dorsal fronto-parietal stream integrates acoustic speech signals with motor-articulatory representations. In Hickock and Poeppel's model the middle and posterior parts of STG are involved in processing of sublexical representations such as phonemes and syllables. Therefore, the MdLF, by virtue of connecting the STG with the AG, may play a role in coding of sublexical representations into articulatory forms and in acoustic-phonetic processing of words and word production.

Possible functional role of MdLF in visuospatial and attention functions—The most prominent pattern of MdLF connections in the right hemisphere and the second most prominent pattern in the left, indicated the SPL relevance (Thiebaut de Schotten et al.) in this fiber's tract role, which along with the AG, would play an important role in visuospatial attention, a dominant function of the right hemisphere (Heilman and Van Den Abell 1980). The superior parietal lobule also codes the location of body parts in a body-centered coordinate system as well as the location of objects in space thus establishing the relative location of objects to the body (see e.g., Duffy and Burchfiel 1971; Lacquaniti et al. 1995; Mountcastle et al. 1975; Sakata et al. 1973). Thus, the MdLF may be related to visuospatial and attentional processing.

Possible functional role of MdLF in high order auditory association functions—One of the most constant characteristics of MdLF is its connection with the temporal pole (TP). Specifically, the fibers of MdLF seem to penetrate in the dorsal part of TP (BA 38) (Figures 2a, 5 and 6), in a region rostral to von Economo's area TA, which corresponds roughly to areas TAr and TAp (Ding et al. 2009). In the experimental animal, TAr has been shown to be related to high order auditory association processing (Poremba et al. 2003). By contrast, TAp is a polysensory association cortical region (Bruce et al. 1981; Seltzer and Pandya 1978; Seltzer and Pandya 1991), which shows responses to both auditory and visual stimuli in monkeys (Poremba et al. 2003). Interestingly, in humans, it has been recently shown to involve SPL in integrative functions of audio-visual multisensory information (Molholm et al. 2006). Thus MdLF connecting the TP with AG and SPL (Figures 3A and 6), could play a role in integrating auditory with visual information.

Clinical implications

The MdLF by virtue of its connections with the superior temporal and angular gyri and, possibly with the temporal pole and superior parietal lobule may be involved in a number of

neurological and psychiatric conditions. More specifically, left STG abnormalities may implicate MdLF in schizophrenia (see e.g., Makris et al. 2010; Rajarethinam et al. 2004) and aphasic syndromes, whereas right STG and AG alterations may involve the MdLF in Attention-Deficit/Hyperactivity Disorder (ADHD) (see e.g., Makris et al. 2007). MdLF may also be implicated in temporal pole and STG pathology observed in primary progressive aphasia (Sapolsky et al. 2010).

Quantitative analyses

Tract volumes, length, mean FA, mean AD, and mean RD of the left and right MdLF in 39 healthy human subjects are shown in Table 2. The overall mean volume of MdLF was 4.12 cm³ (4.06 cm³ on the left, and 4.19 cm³ on the right). These values are similar and thus corroborate previous observations by our group performed in a smaller number of subjects, in which the overall volume of the MdLF was found to be 4.55 cm³ (Makris et al. 2009). MdLF occupies approximately 1.1% of total cerebral white matter, which has been estimated to be 432.47 cm³ (Makris et al. 1999). Compared with other long association fiber tracts, MdLF has roughly the same size as SLF III. It is smaller than the cingulum bundle and the SLF II, and larger than the superior occipitofrontal fascicle (Makris et al. 2009). The MdLF mean FA was .389 on the left and .395 on the right, which were similar to the FA reported in a previous study of MdLF (Makris et al. 2009) and in other studies of different fiber tracts in the normal human brain (Klingberg et al. 2000; Pierpaoli and Basser 1996). MdLF is a long fiber tract, approximately 17 (+/-3.1) cm in the left and 16.6 (+/-3.9) cm in the right hemisphere spanning from the occipital lobe to the temporal pole.

Analysis of symmetry—The MdLF showed minor leftward volumetric and FA asymmetry, which was not statistically significant and was symmetrical for other biophysical parameters such as AD and RD. Given that the MdLF may be involved in language in the left hemisphere but may also play a prominent role in visuospatial attention function in the right hemisphere, it is possible the left and right MdLFs are equally robust structurally and, therefore, show no significant laterality difference in their biophysical characteristics.

Limitations and future studies

Several limitations should be considered when interpreting results of this study. First, even though our sample size is relatively large for imaging studies, probabilities of certain connections might change significantly if larger populations are studied. Second, our results are based on a group containing predominantly males, and thus should not be considered representative for female brains. Third, although our diffusion data are of high quality and high resolution, nonetheless the majority of limitations of the methodology still apply here, i.e., DTI detects and measures water behavior in extracellular space only, making diffusion measures only indirectly related to tract integrity and/or orientation. Each image element (voxel) contains thousands of axons, which means that tractography, by virtue of following the averaged principal diffusion direction, can misrepresent actual tract anatomy either by generating non-existing fibers or by missing existing fibers due to premature interruptions, especially in areas where multiple axons or tracts cross. These limitations may have influenced our observations regarding the variability of MdLF connections in general and the less frequently observed ones, which involved SMG and the occipital lobe, in particular. Thus it appears relevant to differentiate neighboring fiber tracts from each other such as the AF and EmC or IFOF from MdLF. Although we accomplished this satisfactorily, it may be that due to the tortuous shape of AF fibers in the parietotemporal regions and convergence of fibers from the MdLF and EmC or IFOF caudal to the posteriormost insular region, which increases the probability of intravoxel contributions of fibers pertaining to different fiber tracts in these region, the differentiation between these fiber pathways is not precise but

approximate. Furthermore, the known lateralized pattern of the dorsal part of the Sylvian fissure, which is generally steeper in the right hemisphere (Rubens et al. 1976), may have affected our observations with respect to lateralization of MdLF connections. Moreover, regarding the approach used herein for the selection of the MdLF “seed” ROIs in the STG some further explanation is needed. The three “seeds” were sampled in the native space and were spaced at specific intervals measured in slices. The positioning of the “seed” ROIs in absolute terms simplified significantly this method from an anatomical perspective and our results showed that the three ROIs were always positioned within the anterior half of the STG. However, it should be pointed out that this approach may not result as consistent in individuals with uncommon or abnormal anatomy of the STG. Thus it is advisable that, when used in clinical populations this method should be adjusted in a way that “seed” ROIs for the generation of MdLF remain located within the anterior portion of STG. Future studies using a larger number of subjects as well as enhanced MR technology may elucidate more precisely the patterns of connections of MdLF. The MdLF and its strong connections with the angular gyrus and STG may be critical components of the language system in the dominant hemisphere (Dejerine 1895; Geschwind and Galaburda 1987). Then again, the MdLF and its significant connections with the superior parietal lobule, the angular gyrus and STG on the non-dominant hemisphere could be important parts of the visuospatial attention system (Heilman and Van Den Abell 1980; Thiebaut de Schotten et al. 2011b). Future studies using specific language and attention paradigms and implementing multimodal neuroimaging procedures of functional (such as functional MRI and/or magnetoencephalography) and structural MRI (such as T1-MRI and diffusion imaging) may provide further elucidation of the role of MdLF in human cognition.

Conclusion

Based on DTI tractographic analysis we delineated and quantified the MdLF in thirty-nine right-handed healthy adult volunteers, the largest population in which this recently discovered human fiber tract has been studied to date. Compared to previous studies in humans and non-human primates, we found salient differences in cortical connections of the MdLF in humans. The strongest connections of the MdLF were principally with temporal pole, superior temporal gyrus, angular gyrus and superior parietal lobule. A critical finding of this investigation was that these connections were lateralized. While the predominant pattern of connections in the dominant hemisphere, was between the TP, STG and AG as previously reported, in the non-dominant hemisphere the most frequently observed connections were between TP, STG and SPL. Based on the functional roles of the cortical areas that are interconnected by the MdLF in humans, we suggest that this fiber system may be related to language, high order auditory association, visuospatial and attention functions.

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Figure 1. Method used to sample the seed for tractographic growing of the MdLF (green), which is shown in a lateral view of the left hemisphere of a representative subject. Three ROIs that included the entire white matter of the STG were drawn on the FA map as depicted in coronal images 1, 2 and 3 in the bottom row.

Figure 2.

Delineation (2A) and differentiation (2B) of the middle longitudinal fascicle (MdLF). In 2A, the delineation of MdLF in the left hemisphere of a representative subject is shown in detail in five consecutive coronal sections (i-v) indicated on a parasagittal slice in the rostrocaudal dimension. In 2Ai, MdLF is present in the dorsal region (light green) of the temporal pole (TP). Further dorsally, 2Aii and 2Aiii, the MdLF is located within the superior temporal gyrus (STG), whereas in 2Aiv and 2Av, the MdLF is within the angular gyrus (AG). The lateral position of AG with respect to the intraparietal sulcus (inpars) guarantees the lateral location of AG in contrast to the medial location of the superior parietal lobule. In 2B, we show in a lateral view of the left hemisphere in a representative subject, all long association

cortico-cortical fiber pathways in the hemisphere. Specifically, the MdLF, arcuate fascicle (AF), which courses adjacent and lateral to MdLF, the superior longitudinal fascicle II (SLF II) and superior longitudinal fascicle III (SLF III), extreme capsule/inferior frontooccipital fascicle (EmC/IFOF), inferior longitudinal fascicle (ILF), superior occipitofrontal fascicle (SFOF), uncinate fascicle (UF), and cingulum bundle (CB).

Figure 3.

The predominant patterns of MdlF connections are shown in the left and right hemispheres of the same subject. The difference between left temporal pole (TP), superior temporal gyrus (STG) and angular gyrus (AG) pattern and the right TP, STG and superior parietal lobule (SPL) pattern is illustrated with clarity. It is noticeable how the MdlF is following a lower trajectory in the left hemisphere heading towards the angular gyrus, whereas on the right it pursues a higher route entering in the superior parietal lobule. A critical morphologically recognizable anatomical landmark using MRI for the differentiation of AG from SPL is the intraparietal sulcus (inpars), which constitutes a natural border of these two cortical regions, leaving AG on its lateral and SPL on its medial side.

Figure 4.

Views of merged virtual tracts of all subjects. 4A. After merging the left and right MdLF tract from every subject, the resultant MdLF fiber bundle is shown. Panel “a” shows the frontal view, panel “b” shows the caudal view, panel “c” is the dorsal view, panel “d” is the ventral aspect and panels “e” and “f” show the lateral aspects of the right and left hemispheres respectively. 4B. Connections of all virtual fibers with cortical regions are illustrated. The MNI152 brain has been parcellated following the morphometric method of the Center for Morphometric Analysis at Massachusetts General Hospital (Caviness et al. 1996; Rademacher et al. 1992).

Figure 5.

Frontal, lateral and inner views of merged virtual tracts of all subjects with cortical regions the tracts are connected to in the MNI152 standard coordinate space. In 5A, a frontal view shows all connections of MdLF observed in this study of 39 subjects (78 hemispheres) within the cerebral cortex. These are the temporal pole (TP), superior temporal gyrus (STG), supramarginal gyrus (SMG), superior parietal lobule (SPL), precuneus (PCN), temporo-occipital (T-O) and occipital lobe (OCC). Please note that in these cortical regions the angular gyrus should be included, which is a major connection of MdLF, however, is not visible in this frontal view, because it is covered by the SMG. The left and right temporal poles are magnified in the two sides of the figure to emphasize the prominent connection of

MdLF within the dorsal region of the pole, which are readily visible in frontal views. In 5B, lateral and inner views show all cortical connections of MdLF observed in the left and right hemispheres. Although different in nature between right and left, the overall cortical regions involved are similar in both hemispheres and involve the temporal pole (TP), superior temporal gyrus (STG), supramarginal gyrus (SMG), superior parietal lobule (SPL), temporo-occipital region (T-O) and occipital lobe (OCC). Please note that in these cortical regions the precuneus (PCN; dark blue) should be included, which is not as visible in lateral or inner views, because covered by other structures. To allow visualization of more precise fiber-cortex relationships, the MNI152 brain has been parcellated following the morphometric method of the Center for Morphometric Analysis at Massachusetts General Hospital (Caviness et al. 1996; Rademacher et al. 1992).

Figure 6.

Most frequently observed patterns of MdLF connections on the left and right hemispheres in 39 subjects (39 left and 39 right hemispheres) in the MNI152 standard coordinate space. To allow visualization of more precise fiber-cortex relationships, the MNI152 brain has been parcellated following the morphometric method of the Center for Morphometric Analysis at Massachusetts General Hospital (Caviness et al. 1996; Rademacher et al. 1992). Figure 6Ai-iv illustrates the most common pattern of MdLF in the left hemisphere (31%, i.e., 12 of 39 cases). In this pattern, the temporal pole (TP), superior temporal gyrus (STG) and angular gyrus (AG, BA 39), are connected by MdLF. In the bottom row, virtual fibers of MdLF (white) are clearly shown penetrating the AG and the dorsal part of TP. Figure 6Av-vii

shows the second most common pattern of MdLF in the left hemisphere (13%, i.e., 5 of 39 cases). In this pattern, the TP, STG and superior parietal lobule (SPL, BA 7) are connected by MdLF. Virtual fibers of MdLF (white) are clearly shown penetrating the SPL and AG in a magnified detail. Figure 6Aviii-x depicts the third most common pattern of MdLF in the left hemisphere (8%, i.e., 3 of 39 cases). In this pattern, the TP, STG, supramarginal gyrus (SMG, BA 40) and AG (BA 39), are connected by MdLF. Virtual fibers of MdLF are shown penetrating clearly the SMG and AG in a magnified detail. Figure 6Bi-iv illustrates the most common pattern of MdLF in the right hemisphere (18%, i.e., 7 of 39 cases). In this pattern the TP, STG and SPL (BA 7), are connected by MdLF. In the bottom row, virtual fibers of MdLF are clearly shown penetrating the dorsal part of TP and the SPL in a magnified detail. Figure 6B v-vii shows the second most common pattern of MdLF in the right hemisphere (10%, i.e., 4 of 39 cases). Here, the TP, STG, AG (BA 39) and SPL (BA 7) are connected by MdLF. Virtual fibers of MdLF are clearly shown penetrating the AG and SPL in a magnified detail. Figure 6Bviii-x portrays an equally frequent pattern of MdLF in the right hemisphere as the one before (10%, i.e., 4 of 39 cases). Here, the TP, STG and AG (BA 39) are connected by MdLF. Virtual fibers of MdLF are clearly shown penetrating the AG in a magnified detail.

Figure 7.

Composite representations of the “seed” of the MdLF in 39 subjects in the Talairach space in left and right sagittal views. Three ROIs made up the seed in each hemisphere, namely an anterior ROI, a middle ROI and a posterior ROI. The Talairach coordinates (X = medio-lateral axis; Y = anterior-posterior axis; Z = vertical axis) of the center of mass of each ROI were as follows. Right anterior ROI: X = 52.2, Y = -8.3, Z = -2.4; right middle ROI: X = 51.1, Y = -16.6, Z = 2.9; right posterior ROI: X = 51.2, Y = -24.6, Z = 7.9. Left anterior ROI: X = -50.2, Y = -9.7, Z = -2.1; left middle ROI: X = -49.6, Y = -18.1, Z = 3.0; left posterior ROI: X = -48.7, Y = -26.2, Z = 7.4.

Table 1

a. The connectivity pattern of MdLF in the right and left hemisphere for each subject.

Subject (Gender)	Left Hemisphere								Right Hemisphere							
	TP	STG	AG	SMG	SPL	PCN	T-O	OCC	TP	STG	AG	SMG	SPL	PCN	T-O	OCC
1 (M)	+	+	+	-	-	-	-	-	+	+	-	+	+	-	-	-
2 (M)	+	+	+	-	+	-	-	+	-	+	+	-	+	+	-	-
3 (M)	-	+	-	-	-	+	-	-	+	+	-	-	-	+	-	-
4 (M)	+	+	+	-	-	-	-	-	+	+	+	-	-	-	+	-
5 (M)	-	+	+	-	-	-	-	-	+	+	-	-	-	-	-	-
6 (M)	+	+	+	-	-	-	-	-	+	+	+	-	+	-	-	-
7 (M)	+	+	+	-	-	-	-	-	+	+	-	-	+	+	-	-
8 (M)	+	+	+	-	-	-	-	-	+	+	+	-	-	-	-	-
9 (M)	+	+	-	+	+	+	-	-	+	+	-	-	+	+	-	-
10 (M)	+	+	+	-	+	-	-	-	+	+	-	-	+	-	-	-
11 (M)	+	+	+	-	+	+	+	+	+	+	-	-	+	+	-	-
12 (M)	+	+	+	-	+	+	-	-	-	+	+	-	+	+	-	-
13 (M)	-	+	+	-	+	+	-	-	+	+	+	-	+	+	-	-
14 (M)	+	+	+	+	-	-	-	-	+	+	-	-	+	+	+	-
15 (M)	+	+	+	-	-	+	-	+	+	+	+	+	-	+	-	-
16 (M)	+	+	+	-	-	-	-	+	+	+	-	-	+	-	-	-
17 (M)	+	+	+	-	-	-	-	-	+	+	+	-	+	-	-	-
18 (M)	+	+	-	-	-	-	-	+	+	+	-	-	+	-	-	+
19 (M)	-	+	+	-	-	-	-	-	+	+	-	-	+	-	-	-
20 (M)	+	+	+	-	-	-	-	-	-	+	-	-	-	-	+	-
21 (M)	+	+	-	-	-	-	-	-	+	+	+	-	-	-	-	+
22 (M)	+	+	+	-	-	-	-	-	+	+	-	-	+	-	-	-
23 (M)	+	+	+	-	-	+	-	+	+	+	-	-	+	-	-	-
24 (M)	+	+	+	-	-	-	-	-	+	+	+	-	-	-	-	+
25 (M)	+	+	+	+	-	-	-	-	+	+	-	-	-	-	-	-
26 (M)	+	+	+	-	+	-	-	-	+	+	-	-	+	-	-	-
27 (M)	-	+	+	-	-	-	-	-	+	+	-	-	-	-	-	-

a. The connectivity pattern of MdLF in the right and left hemisphere for each subject.

Subject (Gender)	Left Hemisphere								Right Hemisphere							
	TP	STG	AG	SMG	SPL	PCN	T-O	OCC	TP	STG	AG	SMG	SPL	PCN	T-O	OCC
28 (F)	+	+	+	+	-	-	-	-	+	+	-	+	-	-	-	-
29 (M)	+	+	+	-	+	+	-	-	+	+	+	-	+	+	-	+
30 (M)	+	+	-	-	-	+	-	-	+	+	-	-	+	-	-	-
31 (M)	+	+	+	-	-	-	-	-	+	+	+	-	-	-	-	-
32 (M)	+	+	+	-	+	-	-	-	+	+	-	-	-	-	-	-
33 (M)	+	+	+	-	+	-	-	-	+	+	+	-	-	-	-	-
34 (M)	+	+	+	-	-	+	-	-	+	+	+	-	-	-	-	-
35 (M)	+	+	+	-	-	-	-	-	+	+	+	-	-	+	-	-
36 (F)	+	+	+	-	-	-	-	-	+	+	+	+	-	-	-	-
37 (F)	+	+	+	-	-	-	+	+	+	+	-	-	-	-	-	-
38 (F)	+	+	+	-	+	-	-	-	+	+	+	-	+	-	-	-
39 (M)	+	+	+	-	-	-	+	-	+	+	+	-	+	-	-	-

b. The most frequent patterns of connectivity for MdLF in the right and left hemispheres (N=39)

Pus	Left			Right		
	N	%	PU _s	N	%	PU _s
TP STG AG (*)	12	31	TP STG SPL	7	18	
TP STG SPL	5	13	TP STG AG SPL (*)	4	10	
TP STG AG SMG (*)	3	8	TP STG AG	4	10	

The most frequent patterns of connectivity for MdLF in the right and left hemispheres are shaded. Abbreviations: TP = temporal pole; STG = superior temporal gyrus; AG = angular gyrus; SMG = supramarginal gyrus; SPL = superior parietal lobule; PCN = precuneus; T-O = temporo-occipital; OCC = occipital; M = male; F = female; + = present; - = absent.

(*) Indicates the presence of one female subject in the connectivity pattern.

Abbreviations: PU = parcellation unit; TP = temporal pole; STG = superior temporal gyrus; AG = angular gyrus; SPL = superior parietal lobule; SMG = supramarginal gyrus.

Table 2

Measures of volume, fractional anisotropy, axial diffusivity, radial diffusivity and length of the left and center MdLF in 39 healthy human subjects. Symmetry index of these characteristics is also reported herein.

Subject (Gender)	Volume (cm ³)			FA			AD			RD			Length (cm)		
	Left	Center	SI	Left	Center	SI	Left	Center	SI	Left	Center	SI	Left	Center	SI
1 (M)	4.26	5.49	-0.253	396.44	406.51	-0.025	1248.07	1279.33	-0.025	661.51	659.84	0.003	19.71	20.78	-0.053
2 (M)	6.00	4.23	0.345	396.54	424.53	-0.068	1239.51	1313.79	-0.058	657.12	654.07	0.005	18.77	22.26	-0.170
3 (M)	4.00	3.31	0.188	353.85	366.42	-0.035	1279.27	1231.41	0.038	730.78	689.73	0.058	12.68	12.65	0.002
4 (M)	2.53	4.77	-0.614	388.27	396.53	-0.021	1209.85	1278.03	-0.055	658.49	671.21	-0.019	14.08	20.67	-0.379
5 (M)	3.52	2.05	0.525	411.03	384.24	0.067	1336.39	1240.47	0.074	693.61	695.21	-0.002	20.22	7.89	0.877
6 (M)	5.48	4.89	0.113	425.41	409.46	0.038	1269.78	1232.10	0.030	633.07	641.37	-0.013	22.73	18.37	0.212
7 (M)	3.16	2.60	0.195	330.58	378.43	-0.135	1267.38	1265.31	0.002	750.42	704.00	0.064	15.50	15.68	-0.011
8 (M)	3.85	3.10	0.215	353.31	343.32	0.029	1283.12	1332.29	-0.038	732.87	771.85	-0.052	14.19	17.13	-0.188
9 (M)	6.38	9.68	-0.411	417.93	448.10	-0.070	1255.03	1324.85	-0.054	635.89	630.76	0.008	22.12	25.02	-0.123
10 (M)	2.42	2.59	-0.066	358.96	348.40	0.030	1245.63	1255.21	-0.008	704.47	729.51	-0.035	15.28	13.49	0.125
11 (M)	6.41	3.38	0.620	396.71	393.89	0.007	1220.12	1225.07	-0.004	644.18	656.94	-0.020	17.68	14.58	0.192
12 (M)	4.17	4.43	-0.061	392.77	407.15	-0.036	1268.15	1154.19	0.094	678.33	615.35	0.097	17.88	12.40	0.362
13 (M)	5.54	5.76	-0.038	399.97	444.47	-0.105	1248.78	1230.93	0.014	650.06	601.44	0.078	18.28	19.79	-0.079
14 (M)	3.84	4.95	-0.254	351.17	385.58	-0.093	1241.32	1255.86	-0.012	715.71	679.73	0.052	17.43	19.17	-0.096
15 (M)	3.74	6.39	-0.524	426.15	448.56	-0.051	1247.17	1291.05	-0.035	624.38	618.88	0.009	19.41	22.02	-0.126
16 (M)	3.71	3.55	0.044	393.89	403.38	-0.024	1227.23	1221.11	0.005	652.94	642.86	0.016	13.95	14.14	-0.013
17 (M)	2.57	4.09	-0.454	346.46	362.54	-0.045	1184.29	1260.83	-0.063	689.77	713.36	-0.034	11.82	13.15	-0.107
18 (M)	4.91	5.61	-0.133	377.16	393.63	-0.043	1191.60	1223.31	-0.026	649.34	658.65	-0.014	12.11	17.92	-0.388
19 (M)	2.62	4.08	-0.437	352.89	364.66	-0.033	1170.36	1188.56	-0.015	676.06	672.65	0.005	13.78	14.10	-0.023
20 (M)	4.36	2.36	0.597	398.27	371.36	0.070	1406.84	1384.77	0.016	736.13	774.75	-0.051	19.62	12.07	0.476
21 (M)	3.07	5.47	-0.561	371.15	385.57	-0.038	1195.85	1239.41	-0.036	666.11	665.19	0.001	14.18	18.87	-0.284
22 (M)	4.35	4.05	0.072	395.86	407.01	-0.028	1175.85	1193.56	-0.015	622.91	624.39	-0.002	17.02	16.12	0.054
23 (M)	4.03	3.88	0.038	394.32	380.93	0.035	1288.19	1300.75	-0.010	680.81	709.10	-0.041	19.36	20.12	-0.039
24 (M)	3.49	2.20	0.453	383.86	367.58	0.043	1292.42	1257.58	0.027	702.31	699.70	0.004	17.06	21.12	-0.213
25 (M)	3.76	3.33	0.121	383.15	384.21	-0.003	1145.12	1145.06	0.000	621.86	631.92	-0.016	12.57	11.89	0.056
26 (M)	2.95	2.54	0.150	424.84	379.87	0.112	1206.61	1119.82	0.075	612.34	623.68	-0.018	23.47	9.50	0.848

Subject (Gender)	Volume (cm ³)			FA			AD			RD			Length (cm)		
	Left	Center	SI	Left	Center	SI	Left	Center	SI	Left	Center	SI	Left	Center	SI
27 (M)	4.36	3.52	0.215	382.68	404.27	-0.055	1213.66	1253.03	-0.032	657.76	657.03	0.001	20.61	15.99	0.252
28 (F)	6.18	3.46	0.564	393.75	366.80	0.071	1241.80	1220.17	0.018	657.19	683.33	-0.039	18.88	14.31	0.276
29 (M)	3.95	3.84	0.028	440.56	417.83	0.053	1234.22	1134.96	0.084	596.92	583.50	0.023	20.09	20.77	-0.034
30 (M)	3.68	3.82	-0.037	368.14	383.50	-0.041	1219.92	1242.63	-0.018	673.51	672.44	0.002	12.66	14.16	-0.112
31 (M)	3.26	3.58	-0.095	389.67	368.01	0.057	1333.26	1311.06	0.017	709.07	734.64	-0.035	16.33	15.85	0.030
32 (M)	3.35	3.79	-0.122	404.28	423.71	-0.047	1281.03	1294.64	-0.011	666.38	653.85	0.019	21.05	17.09	0.208
33 (M)	4.35	4.77	-0.093	409.43	408.69	0.002	1309.90	1335.13	-0.019	676.27	691.50	-0.022	16.85	16.66	0.011
34 (M)	4.92	3.12	0.446	393.51	396.84	-0.008	1282.19	1266.55	0.012	675.83	677.86	-0.003	17.61	16.71	0.052
35 (M)	3.92	4.86	-0.214	369.81	366.43	0.009	1298.66	1254.23	0.035	720.33	702.69	0.025	17.57	14.98	0.159
36 (F)	3.99	5.19	-0.262	408.44	418.32	-0.024	1217.42	1206.12	0.009	634.37	613.71	0.033	16.44	19.75	-0.183
37 (F)	4.62	3.54	0.264	395.96	400.07	-0.010	1277.83	1263.38	0.011	667.26	672.20	-0.007	16.34	10.95	0.395
38 (F)	2.51	3.74	-0.393	408.36	403.25	0.013	1250.38	1209.40	0.033	649.57	630.20	0.030	16.29	16.23	0.004
39 (M)	4.23	7.30	-0.532	386.72	443.23	-0.136	1242.65	1270.27	-0.022	673.45	631.44	0.064	12.24	22.12	-0.575
Mean	4.06	4.19	-0.030	389.03	394.55	-0.014	1249.92	1248.88	0.001	670.24	667.71	0.004	17.02	16.58	0.027
SD	1.06	1.48	0.34	24.44	26.57	0.06	50.33	56.21	0.04	36.32	43.26	0.04	3.11	3.88	0.29

Abbreviations: SI = symmetry index; FA = fractional anisotropy, AD = axial diffusivity; RD = radial diffusivity; SD = standard deviation; M = male; F = female.