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Human middle longitudinal fascicle: Segregation and behavioral-clinical implications of two distinct fiber connections linking temporal pole and superior temporal gyrus with the angular gyrus or superior parietal lobule using multi-tensor tractography

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Abstract

The middle longitudinal fascicle (MdLF) is a major fiber connection running principally between the superior temporal gyrus and the parietal lobe, neocortical regions of great biological and clinical interest. Although one of the most prominent cerebral association fiber tracts it has only recently been discovered in humans. In this high angular resolution diffusion imaging (HARDI) MRI study, we delineated the two major fiber connections of the human MdLF, by examining morphology, topography, cortical connections, biophysical measures, volume and length in seventy-four brains. These two fiber connections course together through the dorsal temporal pole and the superior temporal gyrus maintaining a characteristic topographic relationship in the mediolateral and ventrodorsal dimensions. As these pathways course towards the parietal lobe, they split to form separate fiber pathways, one following a ventrolateral trajectory and connecting with the angular gyrus and the other following a dorsomedial route and connecting with the superior parietal lobule. Based on the functions of their cortical affiliations, we suggest that the superior temporal-angular connection of the MdLF, i.e., STG(MdLF)AG plays a role in language and attention, whereas the superior temporal-superior parietal connection of the MdLF, i.e., STG(MdLF)SPL is involved in visuospatial and integrative audiovisual functions. Furthermore, the MdLF may have clinical implications in neurodegenerative disorders such as primary progressive aphasia, frontotemporal dementia, posterior cortical atrophy, corticobulbar

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degeneration and Alzheimer's disease as well as attention-deficit/hyperactivity disorder and schizophrenia.

Keywords

High-angular resolution diffusion imaging; Middle longitudinal fascicle; Middle longitudinal fasciculus; Angular gyrus; Superior parietal lobule; Primary progressive aphasia; Neurodegenerative disorders

Introduction

The human middle longitudinal fascicle (MdLF) is a prominent association cortico-cortical fiber pathway connecting the superior temporal gyrus (STG, BA 22, 42) and dorsal temporal pole (TP, BA 38) principally with the angular gyrus (AG, BA 39) (N. Makris 1999; N. Makris et al. 2009; N. Makris et al. 2012) and superior parietal lobule (SPL, BA 7) (N. Makris et al. 2012; Wang et al. 2012). Although a fiber tract of distinct size and location in the human brain, the MdLF was not identified by classical neuroanatomical examinations using gross dissection, secondary degeneration, staining and fixation (e.g., (Dejerine 1895)) or fiber dissection techniques (e.g., (Ludwig and Klingler 1956)), during the past two centuries and was only recently discovered (N. Makris et al. 1999; N. Makris et al. 2009).

In the rhesus monkey, the MdLF was originally described by Seltzer and Pandya using autoradiography (Seltzer and Pandya 1984). These investigators traced MdLF from the inferior parietal lobule (area PG-Opt) following its course rostrally and ventrally within the white matter of the STG to its terminations in areas TPO, PGa and IPa along the upper bank and depth of the superior temporal sulcus (Seltzer and Pandya 1984; Schmahmann and Pandya 2006). Recent diffusion spectrum imaging (DSI) tractography studies also demonstrated the MdLF in the rhesus monkey (Schmahmann et al. 2007).

In humans, the middle longitudinal fascicle was first identified by preliminary histological observations by Makris (1999) (N. Makris 1999), and described as a connection between the STG and the inferior parietal lobule. Subsequent studies used diffusion tensor imaging (DTI) tractography (N. Makris et al. 2009) to demonstrate that the MdLF courses through the superior temporal gyrus and inferior parietal lobule connecting STG (BA 22, 42) and temporal pole (TP, BA 38) principally with the angular gyrus (AG, BA 39). Two very recent reports by Makris and colleagues using streamline DTI tractography (N. Makris et al. 2012) and by Wang and colleagues using diffusion spectrum imaging (DSI) tractography and fiber microdissection (Wang et al. 2012) have expanded our understanding of MdLF and elucidated a number of other connections within the parietal and occipital lobes, particularly emphasizing the superior parietal lobule (SPL, BA 7) connection of the MdLF. Although to a lesser extent, MdLF fibers also connect with several other postrolandic regions, namely the supramarginal gyrus (SMG, BA 40) (N. Makris et al. 2012), precuneus (PCN, BA 7) (N. Makris et al. 2012; Wang et al. 2012), cuneus (CN, BA 18 and BA 19) (N. Makris et al. 2012; Wang et al. 2012), temporo-occipital region (caudal BA 21 and BA 37) (N. Makris et al. 2012) and lateral occipital cortex (BA 18 and 19) (N. Makris et al. 2012). Although they agree in some regards, the reports of these two groups differ significantly. Whereas Makris and colleagues (N. Makris et al. 2012) describe the MdLF as a major fiber connection for the STG and dorsal TP to both, the AG and SPL, Wang and colleagues (Wang et al. 2012) propose that it serves as a major connection only for the TP, STG and SPL with only minor connection to the AG.

Whereas these studies have been relevant for the discovery and current anatomical definition of MdLF in humans, they also presented weaknesses. Specifically, the studies by Makris (1999) and Makris and colleagues (2009) were underpowered, the former based on histological data of one subject and the latter on DTI data of only four subjects. In their study, Wang and colleagues (2012) used DSI/high angular resolution diffusion imaging (HARDI), a technique that offers advantages compared to DTI, however, their study was also underpowered (i.e., six subjects). Finally, although in their study, Makris and colleagues (2012) used a considerably higher number of subjects (i.e., thirty-nine), they used single-tensor based tractography.

Given that the AG (N. Makris et al. 2012) and SPL (N. Makris et al. 2012; Wang et al. 2012) are thought to be the principal connections of the STG and TP with the parietal lobe conveyed by the MdLF, we designed the current study to test the hypothesis that MdLF fibers are present, specifically, either originating or terminating, within the neocortex of the STG, TP, AG and SPL. Thus we performed multi-tensor tractography (Malcolm et al. 2010) in 74 human brains (148 hemispheres) and used a particular approach of diffusion imaging tractography, which made possible the examination of the connections between exclusively and directly selected cortical regions of interest (ROIs). We also hypothesized that the fibers mediating these connections maintain distinct topographic locations within the core of the MdLF. Additionally, we note that the present study includes seventy-four subjects, which is approximately twice the size of our previous investigation of the MdLF. Second, this study uses multi-tensor tractography, which makes it possible to trace through complex fiber architecture, thus offering a novel approach that overcomes the weaknesses of a single-tensor approach as used in our previous study. Third, this study deals with a very relevant issue that has not been addressed previously with the MdLF, namely the direct cortical affiliations of this fiber tract by tracing fiber connections specifically within the gray matter core of the neocortical regions, not just the white matter underlying them. Finally, it provides a clear mapping of the topography of MdLF's two major subdivisions (STG with AG and STG with SPL) and elucidates the importance of both where only one (STG with SPL) has been thought important by Wang and colleagues (Wang et al. 2012).

Methods

We used magnetic multi-tensor based tractography in seventy-four human subjects to accomplish three goals: a) to delineate the principal cortical regions of origin and/or termination of the MdLF within the temporoparietal cortex, specifically the STG, TP, AG and SPL; b) to map the two major subcomponents of the MdLF, that is, the superior temporal-angular or STG(MdLF)AG connection and the superior temporal-superior parietal or STG(MdLF)SPL connection and determine their relative topography within the MdLF; and c) to generate a database based on volume, length and biophysical parameters such as fractional anisotropy (FA) (Basser 2004), axial diffusivity (AD) (Song et al. 2003) and radial diffusivity (RD) (Song et al. 2002; Song et al. 2003) for STG(MdLF)AG and STG(MdLF)SPL. *Terminology* We used the following naming convention to identify the two connections of the MdLF. The fiber pathway (MdLF) appears in parentheses with the gray matter structures it connects to on each side. For instance “STG(MdLF)AG” denotes that the “MdLF” fiber tract connects the “STG” and “AG” gray matter regions; in other words the gray matter regions “STG” and “AG” are connected via the “MdLF” fiber pathway. Likewise, “STG(MdLF)SPL” indicates the MdLF connection that runs between the “STG” and “SPL”. For simplicity, in the terms “STG(MdLF)AG” and “STG(MdLF)SPL”, “STG” includes the dorsal part of temporal pole. This usage is consistent throughout the text, tables and figures.

Subjects

Seventy-four healthy subjects, sixty-two males (mean age = 35.1 ± 12.4) and twelve females (mean age = 24.9 ± 8.7), 17 to 55 years of age (age 34 on average) participated in the study. Of these subjects, seventy-two were right-handed and two left-handed. The average IQ was 113, and none of the subjects presented with diagnosed neurological disorder or history of alcohol or other drug dependency. Subjects were recruited through newspaper advertisements as part of a larger study, and were ascertained to have no Axis I disorder according to the SCID I/NP the Structural Clinical Interview for DSM Disorders (First et al. 1997). This study was approved by the IRBs of both the VA Boston Healthcare System, Brockton Division and Brigham and Women's Hospital. Written informed consent was obtained from all subjects prior to study participation. Thirty-eight of these subjects participated in a previous study published by our group using different anatomical hypotheses, experimental design and methods of diffusion imaging tractographic analysis (N. Makris et al. 2012).

MRI procedures

All subjects were scanned on a 3T GE Echospeed system (General Electric Medical Systems, Milwaukee, WI) using a T1-weighted, T2-weighted and echo planar imaging (EPI) HARDI pulse sequences. The T1-weighted sequence consisted of the following parameters: TR = 7.4 ms, TE = 3 ms, TI = 600, 10° flip angle, 25.6 cm^2 field of view, matrix = 256×256 . The voxel dimensions were $1 \times 1 \times 1 \text{ mm}^3$. The T2-weighted acquisition (namely, eXtended Echo Train Acquisition) produced a series of contiguous images with TR = 2500 ms, TE = 80 ms, 25.6 cm^2 field of view, and voxel dimensions of $1 \times 1 \times 1 \text{ mm}^3$. The HARDI acquisition used a double echo sequence (Alexander et al. 1997; Heid 2000) with an 8-channel coil and ASSET (Array Spatial Sensitivity Encoding Techniques, GE); 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, that is a spatial-spectral pulse was replaced by Fat-Sat suppression pulse, and echo spacing was decreased by 15% to accommodate for more slices per TR. Fifty-one (51) noncollinear 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 $1.7 \times 1.7 \times 1.7 \text{ mm}^3$ voxels. Total scanning time for the HARDI 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 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 3D Slicer software (<http://www.slicer.org>), and then FA, AD and RD were calculated for each voxel.

Cortical parcellation of temporal and parietal regions

To define the cortical ROIs in the temporal and parietal cortices, namely the STG, TP, AG and SPL, we carried out analyses using algorithms in the publicly available FreeSurfer software package (<http://www.martinos.org/freesurfer>) (Fischl et al. 1999; Dale et al. 1999; Fischl and Dale 2000; Fischl et al. 2002; Fischl et al. 2004). The T1-weighted images from each subject were motion-corrected, averaged, and normalized for intensity; subsequently, automated computational reconstruction of brain surface and segmentation of the cortical and subcortical structures were done. Segmentation and automatic labeling of cortical (i.e., cortical parcellation) and subcortical regions (Fischl et al. 2002; Desikan et al. 2006) were done by implementing algorithms as described by Fischl and colleagues (Dale et al. 1999;

Fischl et al. 1999; Fischl and Dale 2000). Finally, the T1 images were registered to the b0 images first rigidly and then implementing a free form deformation field using the Advanced Neuroimaging Tools (ANTs) software (Avants et al. 2008) and the labels were transported using the same deformation. All ROIs identified in our hypotheses, i.e., STG, TP, AG and SPL, were characterized using these methods.

Tractographic delineation of MdLF

Tractography was performed in the 3D Slicer software package (<http://www.slicer.org>, <https://github.com/pnlbwh/ukfractography>), using a multi-tensor tractography algorithm (Malcolm et al. 2010). This algorithm uses tractography to drive the local fiber model estimation, i.e., model estimation (in this case, the multiple tensors) is done while tracing a “fiber” from seed to termination. It must be pointed out that “fiber” is a computational term used throughout this study to denote “virtual fibers”. Because existing techniques independently estimate the model parameters at each voxel (throughout the brain) prior to tractography, there is no running knowledge of confidence in the estimated model fit. Furthermore, noise can significantly affect the estimated model parameters particularly in the case of multi-tensor models, which others including Malcolm and colleagues (Malcolm et al. 2010) and Baumgartner and colleagues (Baumgartner et al. 2012) have compared with existing methods. Malcolm and colleagues (Malcolm et al. 2010) describe an algorithm that formulates fiber tracking as a recursive estimation process, wherein the estimate at each step of tracing the fiber is guided by those previous estimates. In this model, tractography is performed within a filter framework that uses a discrete mixture of Gaussian tensors to model the signal. Starting from a seed point, each fiber is traced to its termination using an unscented Kalman filter to simultaneously fit the local model to the signal and propagate it in the most consistent direction. Despite the presence of noise and uncertainty, this method provides a causal estimate of the local structure at each point along the fiber. Furthermore, because each iteration begins with a near-optimal solution based on the previous estimation, the convergence of model fitting is improved and local minima are naturally avoided. Furthermore, since tractography and model estimation is done simultaneously, we do not need artificial criteria such as critical stopping angle.

Another important aspect of this algorithm is that it provides a measure of confidence (a covariance matrix) in the estimation of the parameters at each step, which can remove false positives in tractography. This approach reduces signal reconstruction error and significantly improves the angular resolution at crossings and branchings. Because it enables detection of two eigenvalues in a voxel, this method resolves the problem of crossing fibers, allowing fiber tracing in areas that are known to contain such crossing and branching (Rathi et al. 2010). White matter voxels in the brain ($FA > 0.15$) were used as seed points for (whole-brain) tractography. We then obtained two different fiber tracts for both hemispheres by selecting only the fibers that passed through specific regions for each MdLF connection. Therefore, we do not require any additional geometric constraints to remove short fibers. For the superior temporal-AG (i.e., STG(MdLF)AG) connection these regions comprised the cortex of the superior temporal gyrus (STG) and temporal pole (TP), cortex of the angular gyrus (AG) and a white matter ROI of STG. For the superior temporal-SPL (i.e., STG(MdLF)SPL) connection, the selected regions were the cortex of the superior temporal gyrus and temporal pole, cortex of the superior parietal lobule (SPL) and a white matter ROI of STG (Figures 1 and 2). Whereas the cortical ROIs in the STG, TP, AG and SPL were determined automatically using FreeSurfer, as noted previously, the STG white matter ROI was defined manually. Specifically, this ROI was set by sampling all voxels within the white matter of the STG in a single coronal section in the rostral one third of the STG, precisely 17 mm caudal to the frontotemporal junction (FTJ), as shown in Figure 1c. It is important to note that FTJ corresponds to $Y = +4$ mm in the rostrocaudal dimension of the Talairach

coordinate space system. Given that the STG spans +4 mm to -55 mm in the Talairach Y rostrocaudal dimension, the white matter STG ROI is located approximately at Y = -13 mm and, thus within the rostral third of STG in Talairach space. This is important for assuring that fibers of the MdLF course through the anterior part of the STG. Therefore, the tractographic approach used in this study had two *necessary* conditions, that is, specification of the cortical ROIs and the white matter ROI. The first condition for selection of the cortical ROIs ensured that only fibers originating and terminating within these temporal and parietal cortical regions could be sampled and any fibers passing through their underlying white matter compartment but not entering or exiting these cortices were excluded. Positioning the white matter ROI only within the STG, which also ensured the sampling of all STG white matter voxels in that coronal section, guaranteed that only fibers coursing within the STG were sampled, hence excluding fibers coursing in adjacent regions such as the extreme capsule (EmC) or the middle temporal gyrus. To ensure the anatomical accuracy of MdLF reconstructions, all cases were inspected and all neighboring long association fiber tracts were delineated in five brains by one of the authors (NM) using procedures previously described by our group (N Makris et al. 2002; N. Makris et al. 2005; N. Makris et al. 2007b; N. Makris et al. 2009; N. Makris and Pandya 2009; N. Makris et al. 2012). Differentiating the MdLF from other fiber tracts such as the EmC, the inferior frontooccipital fascicle (IFOF) and the arcuate fascicle (AF) is critical. The two *necessary* conditions set in this method help to ensure the exclusion of EmC, IFOF and AF fibers.

Probabilistic Mapping of MdLF

We generated probability maps for STG(MdLF)AG and STG(MdLF)SPL in MNI152 standard space (Evans et al. 1993) by first registering each subject to an MNI152 template with a resolution of 1 mm³. The FA map of each subject was registered linearly using FLIRT (Jenkinson and Smith 2001), and then nonlinearly using ANTs (Avants et al. 2008). We then applied the same deformation to the fiber tracts to set them in MNI152 space and calculated a fiber tract mask on the MNI152 template for each subject. In this mask a voxel has a value only if a tract traverses it. Finally, to obtain the probabilistic maps, we averaged the masks of all subjects.

Quantitative Analyses

Measurements of volume, length, mean FA, mean AD and mean RD of the left and the right MdLF were obtained in 74 healthy human subjects (148 middle longitudinal fascicles). The diffusion imaging biophysical parameters of FA, AD and RD may relate to fiber tract coherence and integrity (Basser 2004; Song et al. 2002; Song et al. 2003). *Symmetry index (SI)* ($SI = (Left - Right) / 0.5 (Left + Right)$ (Galaburda et al. 1987)) for left and right MdLF for measures of volume, mean FA, mean AD and mean RD were calculated for each individual, and across subjects.

Results

Delineation of MdLF and its connections

This study demonstrated clear delineation of the MdLF from other neighboring fiber tracts such as the AF, EmC and IFOF as shown in Figure 3, and further, the delineation of the STG(MdLF)AG and STG(MdLF)SPL connections within the MdLF (Figures 1, 2 and 3). With a sample of 74 normal subjects, this is the largest study for the MdLF according to our previous data (N. Makris et al. 2012). Specifically, STG(MdLF)AG connections were ascertained on the left in 68 (92%) subjects and on the right in 69 (93%) subjects. Furthermore, STG(MdLF)SPL connections were ascertained on the left in 56 (76%) subjects and on the right in 65 (88%) subjects. The TP was found to connect on the left in 47 (69%) subjects and on the right in 37 (50%) subjects of the STG(MdLF)AG connections; in

STG(MdLF)SPL connections, the TP connected on the left in 27 (47%) and on the right in 35 (55%) subjects.

Mapping of STG(MdLF)AG and STG(MdLF)SPL

Figure 4 shows the two major subdivisions of the MdLF mapped on the MNI152 standard space. These maps were obtained by averaging tract masks generated from the fiber tracts of all subjects previously registered to the MNI space. The 3D Slicer software environment was used to create these images.

Three-dimensional reconstructions elucidated the relative topography of STG(MdLF)AG and STG(MdLF)SPL within the MdLF. STG(MdLF)AG was located ventrally and laterally with respect to STG(MdLF)SPL, which was positioned dorsally and medially. The two fiber pathways coursed within the dorsal TP and the entire STG white matter as a compact fiber tract showing generally this relative topography. Caudally at the temporoparietal transition of STG the two fiber tracts split and course as separate entities within the parietal lobe. STG(MdLF)AG follows a lateral course penetrating the cortex of AG, whereas STG(MdLF)SPL continues in a dorsomedial trajectory penetrating the cortex of SPL (Figure 5).

Quantitative analysis

We measured biophysical parameters including FA, AD, RD and volume for STG(MdLF)AG and STG(MdLF)SPL, as shown in Table 1. STG(MdLF)AG had a mean volume (left and right) of 4.54 cm³ (2.11 cm³ and 2.43 cm³ on the left and right respectively), mean lengths of 8.72 cm on the left and 8.45 cm on the right; the mean FA was .34 on both the left and right. STG(MdLF)SPL had a total volume (left and right) of 4.07 cm³, i.e., 1.68 cm³ and 2.39 cm³ on the left and right sides respectively, and mean lengths of 10.1 cm on the left and 10.2 cm on the right. The mean FA on both the left and the right was .37.

Analysis of symmetry

Table 1 lists the symmetry index (SI) for the left and right measurements of volume, length, mean FA, mean AD and mean RD in STG(MdLF)AG and STG(MdLF)SPL. Some of these measures, as we explain below, showed significant left-right differences in two-tailed independent sample t-tests. The left STG(MdLF)SPL FA and length measures were greater than those in either the right or left STG(MdLF)AG, while the right STG(MdLF)SPL FA and length were greater than those in the right STG(MdLF)AG. The total overall (i.e., right and left combined) FA and length were greater in STG(MdLF)SPL than in the STG(MdLF)AG. Interestingly, the RD measurements showed the opposite statistically significant pattern; that is, the left STG(MdLF)SPL RD was lower than in either the right or left STG(MdLF)AG, and RD in the right STG(MdLF)SPL was lower than in the right STG(MdLF)AG. The total (right and left combined) RD in STG(MdLF)SPL was lower than the total RD in STG(MdLF)AG. Meanwhile, AD was statistically significantly greater in the left STG(MdLF)SPL than in the right STG(MdLF)SPL or right STG(MdLF)AG. Volumetrically, the right STG(MdLF)AG was statistically significantly larger than the left STG(MdLF)SPL and the right STG(MdLF)SPL was statistically significantly larger than left STG(MdLF)SPL. Furthermore, the entire right side of the MdLF (i.e., right STG(MdLF)AG and right STG(MdLF)SPL combined) was statistically significantly larger than the left MdLF (i.e., left STG(MdLF)AG and left STG(MdLF)SPL combined), even though STG(MdLF)AG (right and left) showed no statistically significant difference compared to STG(MdLF)SPL (right and left).

Discussion

In this study we acquired 74 high-resolution HARDI datasets from normal human subjects, which together allowed us to examine a total of 148 middle longitudinal fascicles with multi-tensor tractography. As we had hypothesized, our data showed that MdLF fibers were present within the neocortex of the STG, TP, AG and SPL regions; furthermore, our data showed that within the MdLF were the two principal connections of (N. Makris et al. 2012) that can be delineated as two distinct fiber pathways, one connecting the superior temporal gyrus with the angular gyrus (i.e., STG(MdLF)AG) and the other connecting the superior temporal gyrus with the superior parietal lobule (i.e., STG(MdLF)SPL). By mapping these pathways on the MNI152 coordinate space we determined their characteristic relative topographic locations within the core of the MdLF as well as their characteristic topography within the STG and lateral parietal lobe. While they appear to share the space within the core of the STG and dorsal TP white matter to a large extent, in the lateral parietal lobe, STG(MdLF)AG clearly occupies the ventrolateral position, while STG(MdLF)SPL lies in the dorsomedial position (Figures 4 and 5). These two fiber connections were comparable in length and biophysical measures, and to a certain extent, were similar in volume (Table 1).

After reviewing the available literature, we find there have been only a few anatomical studies on the human middle longitudinal fascicle. This pathway was proposed as an association fiber tract connecting the posterior STG with the inferior parietal lobule by Makris (1999) (N. Makris 1999) based on preliminary histological observations. In a second study using DTI tractography in four subjects (eight hemispheres), Makris and colleagues (2009) (N. Makris et al. 2009) defined MdLF as a long corticocortical connection between STG and AG. According to the latter study, MdLF courses from the temporal pole (BA 38) throughout the entire superior temporal gyrus (BA 22, 41, 42) to connect with the inferior parietal lobule, especially the angular gyrus (BA 39). These two studies showed agreement with earlier observations in the rhesus monkey where Seltzer and Pandya originally defined the MdLF (Seltzer and Pandya 1984). Furthermore, the STG with AG connection of MdLF in humans was later confirmed by three studies (Turken and Dronkers 2011; Menjot de Champfleury et al. 2013; Asami et al. 2013). Recently, knowledge of MdLF connectivity has been expanded by two studies. Specifically, Makris and colleagues using single-tensor tractography (N. Makris et al. 2012) showed variations in MdLF connections in a sample of 39 subjects. In their study, they demonstrated that the two principal connections of the MdLF are between the dorsal TP (BA 38) and STG (BA 22, 42) and, respectively the AG (BA 39) and SPL (BA 7). Furthermore, they determined other connections with several postrolandic regions in the parietal and occipital lobes such as the supramarginal gyrus (BA 40), precuneus (BA 7), cuneus (BA 18, 19), temporo-occipital region (caudal BA 21 and BA 37) and lateral occipital cortex (BA 18, 19). Another study by Wang and colleagues (Wang et al. 2012) using DSI tractography (Tuch et al. 2002; Wedeen et al. 2008) in six subjects as well as the publicly available NTU-90 DSI atlas (Yeh and Tseng 2011) and complemented by fiber microdissection in four subjects, demonstrated the MdLF connection between TP, STG and SPL (BA 7), precuneus (BA 7) and cuneus (CN, BA 18 and BA 19). The latter studies supported further the concept that due to evolutionary changes human association fiber tracts differ considerably from the monkey (Rilling et al. 2008) and provided substantial evidence in this regard for MdLF in particular. Although the principal findings emerging from these studies were that the STG and TP also connect robustly with the SPL and parietooccipital regions, it is important to point out that there is a critical difference between these two depictions. Whereas Makris and colleagues have shown that the MdLF robustly connects the STG and dorsal TP with both the AG and SPL (N. Makris et al. 2012), Wang and colleagues describe MdLF as a primary connection for TP, STG and SPL only, with minimal connection to AG (Wang et al. 2012).

The two principal connections of MdLF, namely STG(MdLF)AG and STG(MdLF)SPL: topography and quantification

We successfully delineated two distinct corticocortical connections between the STG and dorsal TP with the lateral parietal lobe, specifically with the angular gyrus (i.e., STG(MdLF)AG) and the superior parietal lobule (i.e., STG(MdLF)SPL). These two long fiber pathways were distinctly visible within the core white matter of the dorsal TP and STG. As they coursed caudally in the parietal lobe, they were clearly segregated and connected robustly with the AG and SPL. STG(MdLF)AG was located ventrolaterally and STG(MdLF)SPL dorsomedially, as shown with clarity and in detail in Figures 4 and 5. Furthermore, their intricate spatial relationships are illustrated in a simplified manner by plotting the complete trajectories of all subjects in the Talairach coordinate space as shown in Figure 6 with their complete coordinates reported in the APPENDIX. Length, FA, AD and RD values were overall in agreement with the results from previous studies on MdLF (N. Makris et al. 2009; N. Makris et al. 2012; Wang et al. 2012). Nevertheless, we did find certain statistically significant differences in symmetry between right and left for these fiber tracts. Interestingly, FA, RD and length asymmetries showed a pattern in that they were present for the same pair of comparisons, namely left STG(MdLF)SPL versus the left or right STG(MdLF)AG, right STG(MdLF)SPL versus the right STG(MdLF)AG and total (i.e., left and right combined) STG(MdLF)SPL versus the total STG(MdLF)AG. As expected, FA and length differences were concordant, whereas RD differences were evident in the opposite direction detailed in Results section. Importantly, the significantly larger RD in the left or right STG(MdLF)AG as well as in the total (i.e., left and right combined) STG(MdLF)AG compared to left or right STG(MdLF)SPL or total STG(MdLF)SPL reflected the curved form of STG(MdLF)AG as opposed to the more longitudinal shape of STG(MdLF)SPL. AD comparisons, which showed significantly larger values for left STG(MdLF)SPL versus right STG(MdLF)AG, provide further evidence to support this observation. STG(MdLF)AG (4.54 cm³) was slightly larger than STG(MdLF)SPL (4.07 cm³) in overall (i.e., right plus left) volume. This finding was consistent with the observation that the connection between STG and AG is larger than the connection between STG and SPL in the human brain (N. Makris et al. 2012). Furthermore, STG(MdLF)AG (2.11 cm³) was 25% larger than STG(MdLF)SPL (1.68 cm³) in the left hemisphere, supporting the notion that STG(MdLF)AG is the predominant MdLF connection in the dominant hemisphere and, given its affiliations with the superior temporal and angular gyri, may play a role in language, particularly in sub-lexical processing (Hickok 2001; Hickok and Poeppel 2007; N. Makris et al. 2012). Furthermore, after removing two left handed individuals from the analysis, the STG(MdLF)AG (2.09 cm³) was still larger than the STG(MdLF)SPL (1.65 cm³) in the left hemisphere by 27% and the symmetry ratio did not change significantly. Moreover the right STG(MdLF)SPL (2.39 cm³) was significantly (42%) larger than its left counterpart (1.68 cm³), in agreement with recent reports (N. Makris et al. 2012; Wang et al. 2012), which may indicate a predominant role of the right STG(MdLF)SPL in visuospatial attention (Duffy and Burchfiel 1971; Lacquaniti et al. 1995; Mountcastle et al. 1975; Sakata et al. 1973). In the right hemisphere both, STG(MdLF)AG (2.43 cm³) and STG(MdLF)SPL (2.39 cm³) were large and did not differ significantly in volume, and therefore the right total MdLF (4.82 cm³) was larger overall (by 27%) than the left MdLF (3.79 cm³). The strong right-side prominence of both components of the MdLF suggests the MdLF is involved in attention functions (Heilman and Van Den Abell 1980; Thiebaut de Schotten et al. 2011). The overall volume of the MdLF, i.e., STG(MdLF)AG and STG(MdLF)SPL, right and left combined was measured as 8.6 cm³, similar to the average measurement of 8.25 cm³ in a previous study of a smaller subject sample (N. Makris et al. 2012); the average STG(MdLF)AG volume (4.54 cm³) was also similar to that from a previous comparable study (4.55 cm³) by our group (N. Makris et al. 2009). Interestingly, in the present study we observed more robust bilateral connections between the STG and both, the AG and SPL;

these connections were not as lateralized as in our previous study (N. Makris et al. 2012). Furthermore, in this study the presence of STG connections with AG or SPL was considerably higher than in a recent study of our group (N. Makris et al. 2012). However, the method applied here had two principal differences. First, this study examined a restricted set of connections, exclusively those among the STG, TP, AG and SPL neocortical regions, excluding any fibers ending or passing through white matter regions underneath these cortices or elsewhere in the brain. Second, it implemented a filtered multi-tensor tractography algorithm that differs from the single-tensor tractography approach used previously by our group (N. Makris et al. 2009; N. Makris et al. 2012). In addition to the fact that the sample examined in the present study was considerably larger than in prior studies, these two principal methodological factors may account for the connectional differences observed here. Nevertheless, the almost categorical difference in our observations of the superior temporal-angular connection of MdLF (i.e., STG(MdLF)AG) (between both our findings from the single-tensor tractography study in 39 subjects (N. Makris et al. 2012) and the present multi-tensor tractographic analyses on 74 subjects) and the DSI tractography analysis in six subjects and NTU-90 atlas analysis by Wang and colleagues (Wang et al. 2012; Yeh and Tseng 2011), remains an important unresolved issue to address. We concur with Wang and colleagues (Wang et al. 2012) that direct comparisons of diffusion imaging datasets of the identical subjects should be done to understand the discrepancy between findings using different modalities of diffusion imaging tractographic analyses of the MdLF in the human brain. This should be done using comparable experimental conditions among the different imaging modalities (such as DTI, DSI or HARDI) in terms of acquisition parameters, spatial resolution and tractographic procedures.

Functional role of MdLF

Separating STG(MdLF)AG from STG(MdLF)SPL, the two principal connections running between the superior temporal regions and the parietal lobe, increases specificity in the anatomical connectivity of MdLF, which could be reflected in functional specificity as well. Although there is no direct functional evidence of the function of the MdLF per se, there are some propositions based on the known functions of the cortical regions it is connected to. As mentioned previously, it has been suggested that STG(MdLF)AG may be related to *language processing* (N. Makris et al. 2009; Turken and Dronkers 2011; N. Makris et al. 2012; Saur et al. 2008; Menjot de Champfleury et al. 2013). More specifically, following the dual stream model of language processing by Hickok and Poeppel (Hickok and Poeppel 2000, 2007), Makris et al. (N. Makris et al. 2012) suggested that MdLF in the dominant hemisphere for language “may play a role in coding of sublexical representations into articulatory forms and in acoustic-phonetic processing of words and word production” (N. Makris et al. 2012). The role of STG(MdLF)AG in language has been debated by De Witt Hamer and colleagues (2011) (De Witt Hamer et al. 2011) based on intraoperative brain electrostimulation findings of no interference with picture naming, whereas Wang and colleagues (Wang et al. 2012) did not support a role for MdLF in language based on their DSI tractography results that showed minimal connections between STG and AG. By contrast, it has been proposed that STG(MdLF)SPL may be involved in *high order auditory association functions* (N. Makris et al. 2012). This assumption is based in part on experimental studies in monkeys demonstrating high order auditory association functions and polysensory (i.e., visual and auditory) processing in temporopolar cortical areas TAR (Poremba et al. 2003) and TAp (Bruce et al. 1981; Seltzer and Pandya 1978, 1991; Poremba et al. 2003) respectively.

Recent observations in humans revealing that SPL is involved in higher order auditory association and integrative audio-visual multisensory processing (Molholm et al. 2006) add credence to the notion that STG(MdLF)SPL by linking temporopolar regions with SPL, may

be an important connection for this integrative function. Furthermore, it has been suggested that STG(MdLF)/SPL could be related to processing of spatial features of sound and thus may represent part of the “where” pathway for the auditory system (Wang et al. 2012). The two principal connections of MdLF seem to subserve several dominant functions in the right hemisphere as well, such as *attention*, and *visuospatial ability*. It has been long known that visuospatial disabilities have been associated with parietooccipital lesions (Heilman and Valenstein 1985) and also that the cortical attention system involves mainly the inferior parietal lobule, the dorsolateral prefrontal region, the cingulate gyrus and the banks of the superior temporal sulcus in humans (Cabeza and Nyberg 2000; Corbetta and Shulman 2002; Critchley 1966; Duncan and Owen 2000; Goldman-Rakic 1988; Heilman et al. 1970; Heilman and Valenstein 1985; Heilman and Van Den Abell 1980; Heilman et al. 1983; Mesulam 1990, 1998; Posner and Petersen 1990; Karnath et al. 2001). Recently, based on a multimodal neuroimaging study using a task of active exploration, Suchan and colleagues suggested that the right STG(MdLG)AG may be involved in spatial orientation and attention (Suchan et al. 2013).

Clinical role of MdLF

The MdLF may have clinical implications for several neurologic and psychiatric conditions involving the dorsal temporal pole, angular gyrus, superior temporal gyrus, and superior parietal lobule. Neurodegenerative diseases affecting these regions include primary progressive aphasia (PPA) (Sapolsky et al. 2010), frontotemporal dementia (Rohrer et al. 2008), Alzheimer’s disease (Dickerson et al. 2009), posterior cortical atrophy (Lehmann et al. 2009), and corticobasal degeneration (Boxer et al. 2006). The semantic variant of PPA, also known as semantic dementia, selectively involves the temporal pole early in its course (Galton et al. 2001); based on our own preliminary data, as the disease progresses, it spreads into orbitofrontal cortex as well as angular gyrus, raising the question of whether connections via uncinate fascicle and MdLF may be critical to the localization of progression. The logopenic variant of PPA selectively affects posterior temporal and inferior parietal regions including angular gyrus, often resulting in a conduction-like or mixed transcortical sensory aphasia early in its course (Gorno-Tempini et al. 2008). Alzheimer’s disease commonly involves all of the key regions connected through the MdLF, resulting in associated semantic and phonologic language impairments, Gerstmann syndrome, apraxias, and visuospatial/attentional symptoms. As neurodegenerative diseases begin to be understood in the context of large-scale brain networks (Seeley et al. 2009), the key large white matter bundles linking spatially distributed cortical regions become of critical interest. This notion applies to other disorders as well such as schizophrenia (see (N. Makris et al. 2010; Rajarethinam et al. 2004)), attention-deficit/hyperactivity disorder (ADHD) (N. Makris et al. 2007a) and neglect syndrome (Heilman and Van Den Abell 1980). In a recent study by our group, it has been suggested that in chronic schizophrenia, MdLF may be structurally altered bilaterally and differentially associated with thought organization deficit on the left and attention deficit on the right hemisphere (Asami et al. 2013).

Limitations and future studies

There are certain limitations that should be considered when interpreting the results of this study. One such limitation we must point out is that of the diffusion imaging methodology itself; namely, that diffusion imaging detects and measures water behavior only in extracellular space, making diffusion measures only indirectly related to tract integrity and/or orientation (Catani et al. 2012; N. Makris et al. 2012). However, our sample of 74 subjects was relatively large and the diffusion data we acquired were of high quality and resolution. Furthermore, filtered multi-tensor tractography (Rathi et al. 2010), which significantly improves the angular resolution at crossings and branchings, allows the tracing of fibers in regions where multiple axons or tracts cross one another resulting in less fiber

truncations, more virtual fibers and more connections as shown in Figure 7. It is interesting that in this study using multi-tensor tractography we obtained stronger results for both, STG(MdLF)AG and STG(MdLF)SPL connections of MdLF than in our previous study using single-tensor tractography (N. Makris et al. 2012). The advantages multi-tensor tractography offers over single-tensor tractography make the former an improved technique for the study of inter-individual variability, a topic of high interest in biology. Again, however, the present study examined a much larger sample, specifically 74 subjects compared to 39 in a previous study by our group (N. Makris et al. 2012). Another possible limitation was that our results were based on a group containing predominantly males (62 males and 12 females) and, therefore should not be considered representative of female brains. Bearing this limitation in mind we examined separately males and females and observed no differences with respect to measurements reported in Table 1. To elucidate the functional roles of STG(MdLF)AG and STG(MdLF)SPL, future studies should employ specific language, visuospatial attention and audiovisual paradigms and implement multimodal neuroimaging procedures that incorporate functional imaging (e.g., functional MRI and/or magnetoencephalography) with structural MRI techniques such as T1-MRI and diffusion imaging. Moreover, future studies with adequately powered samples, should examine issues on gender and handedness, as well as address the question of inter-individual variability to further elucidate whether variability of MdLF connections represents actual individual connectivity differences among subjects, or it reflects one or more methodological factors. Finally, future studies should target specific clinical populations to clarify the clinical role of the different subcomponents of MdLF.

Conclusion

Based on high-resolution filtered multi-tensor tractographic analysis we delineated and quantified the two major components of the MdLF in seventy-four healthy adult volunteers, the largest study of its kind to examine this long association fiber pathway to date. Both connections of the MdLF, that is, the one connecting the STG and dorsal TP with the AG (i.e., STG(MdLF)AG) and the one connecting the STG and dorsal TP with the SPL (i.e., STG(MdLF)SPL) were robust. These connections presented a characteristic topography within the MdLF, with STG(MdLF)AG located more ventrolaterally and STG(MdLF)SPL more dorsomedially. Based on the functional roles of the cortical areas these two fiber tracts are affiliated with in humans, we suggest that STG(MdLF)AG may be related to language and attention, whereas STG(MdLF)SPL to audiovisual integrative and visuospatial functions. Moreover, the MdLF may be involved in several neuropsychiatric conditions such as neurodegenerative diseases, attention-deficit/hyperactivity disorder and schizophrenia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

- Aja-Fernandez S, Niethammer M, Kubicki M, Shenton ME, Westin CF. Restoration of DWI data using a Rician LMMSE estimator. *IEEE Trans Med Imaging*. 2008; 27(10):1389–1403. [PubMed: 18815091]
- Alexander AL, Tsuruda JS, Parker DL. Elimination of eddy current artifacts in diffusion-weighted echo-planar images: the use of bipolar gradients. *Magn Reson Med*. 1997; 38(6):1016–1021. [PubMed: 9402204]
- Asami T, Saito Y, Whitford TJ, Makris N, Niznikiewicz M, McCarley RW, et al. Abnormalities of middle longitudinal fascicle and disorganization in patients with schizophrenia. *Schizophr Res*. 2013; 143(2-3):253–259. [PubMed: 23290607]
- Avants BB, Epstein CL, Grossman M, Gee JC. Symmetric diffeomorphic image registration with cross-correlation: evaluating automated labeling of elderly and neurodegenerative brain. *Med Image Anal*. 2008; 12(1):26–41. [PubMed: 17659998]
- Basser PJ. Scaling laws for myelinated axons derived from an electrotonic core-conductor model. *J Integr Neurosci*. 2004; 3(2):227–244. [PubMed: 15285056]
- Baumgartner, C.; Micahilovich, O.; Pasternak, O.; Levitt, J.; Weston, C-F.; Shenton, ME., et al. A unified tractography framework for comparing diffusion models on clinical scans; Paper presented at the CDMRI-workshop (MICCAI'12); London, UK. 2012.
- Boxer AL, Geschwind MD, Belfor N, Gorno-Tempini ML, Schauer GF, Miller BL, et al. Patterns of brain atrophy that differentiate corticobasal degeneration syndrome from progressive supranuclear palsy. *Arch Neurol*. 2006; 63(1):81–86. [PubMed: 16401739]
- Bruce C, Desimone R, Gross CG. Visual properties of neurons in a polysensory area in superior temporal sulcus of the macaque. *J Neurophysiol*. 1981; 46(2):369–384. [PubMed: 6267219]
- Cabeza R, Nyberg L. Neural bases of learning and memory: functional neuroimaging evidence. *Curr Opin Neurol*. 2000; 13(4):415–421. [PubMed: 10970058]
- Catani M, Bodi I, Dell'Acqua F. Comment on “The geometric structure of the brain fiber pathways”. *Science*. 2012; 337(6102):1605. [PubMed: 23019632]
- Corbetta M, Shulman GL. Control of goal-directed and stimulus-driven attention in the brain. *Nat Rev Neurosci*. 2002; 3(3):201–215. [PubMed: 11994752]
- Critchley M. Is developmental dyslexia the expression of minor cerebral damage? *Clin Proc Child Hosp Dist Columbia*. 1966; 22(8):213–222. [PubMed: 5231793]
- Dale AM, Fischl B, Sereno MI. Cortical surface-based analysis. I. Segmentation and surface reconstruction. *Neuroimage*. 1999; 9(2):179–194. [PubMed: 9931268]
- De Witt Hamer PC, Moritz-Gasser S, Gatignol P, Duffau H. Is the human left middle longitudinal fascicle essential for language? A brain electrostimulation study. *Hum Brain Mapp*. 2011; 32(6):962–973. [PubMed: 20578169]
- Dejerine, J. *Anatomie des Centres Nerveux*. Tome 1. Paris, France: Rueff et Cie; 1895. 1980, Masson ed
- Desikan RS, Segonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage*. 2006; 31(3):968–980. [PubMed: 16530430]
- Dickerson BC, Bakkour A, Salat DH, Feczko E, Pacheco J, Greve DN, et al. The cortical signature of Alzheimer's disease: regionally specific cortical thinning relates to symptom severity in very mild to mild AD dementia and is detectable in asymptomatic amyloid-positive individuals. *Cereb Cortex*. 2009; 19(3):497–510. [PubMed: 18632739]
- Duffy FH, Burchfiel JL. Somatosensory system: organizational hierarchy from single units in monkey area 5. *Science*. 1971; 172(3980):273–275. [PubMed: 4994137]
- Duncan J, Owen AM. Common regions of the human frontal lobe recruited by diverse cognitive demands. *Trends Neurosci*. 2000; 23(10):475–483. [PubMed: 11006464]
- Evans, AC.; Collins, DL.; Mills, SR.; Brown, ED.; Kelly, RL.; Peters, TM. 3D statistical neuroanatomical model from 305 MRI volumes. Nuclear Science Symposium and Medical Imaging Conference, 1993 IEEE Conference Record; 1993. p. 1813-1817.

- First, M.; Spitzer, R.; Gibbon, M.; Williams, J. Structured Clinical Interview for DSM-IV Axis I Disorders. Washington, D.C.: American Psychiatric Press; 1997.
- Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proc Natl Acad Sci U S A*. 2000; 97(20):11050–11055. [PubMed: 10984517]
- Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, et al. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron*. 2002; 33(3):341–355. [PubMed: 11832223]
- Fischl B, Sereno MI, Dale AM. Cortical surface-based analysis. II: Inflation, flattening, and a surface-based coordinate system. *Neuroimage*. 1999; 9(2):195–207. [PubMed: 9931269]
- Fischl B, van der Kouwe A, Destrieux C, Halgren E, Segonne F, Salat DH, et al. Automatically parcellating the human cerebral cortex. *Cereb Cortex*. 2004; 14(1):11–22. [PubMed: 14654453]
- Galaburda AM, Corsiglia J, Rosen GD, Sherman GF. Planum temporale asymmetry, reappraisal since Geschwind and Levitsky. *Neuropsychologia*. 1987; 25(6):853–868.
- Galton CJ, Patterson K, Graham K, Lambon-Ralph MA, Williams G, Antoun N, et al. Differing patterns of temporal atrophy in Alzheimer's disease and semantic dementia. *Neurology*. 2001; 57(2):216–225. [PubMed: 11468305]
- Goldman-Rakic PS. Topography of cognition: parallel distributed networks in primate association cortex. *Annu Rev Neurosci*. 1988; 11:137–156. [PubMed: 3284439]
- Gorno-Tempini ML, Brambati SM, Ginex V, Ogar J, Dronkers NF, Marcone A, et al. The logopenic/phonological variant of primary progressive aphasia. *Neurology*. 2008; 71(16):1227–1234. [PubMed: 18633132]
- Heid, O. *Proc Int Soc Mag Reson Med*. Denver: Denver, CO; 2000. Eddy current-nulled diffusion weighted; p. 799
- Heilman KM, Pandya DN, Geschwind N. Trimodal inattention following parietal lobe ablations. *Trans Am Neurol Assoc*. 1970; 95:259–261. [PubMed: 4998763]
- Heilman, KM.; Valenstein, E. *Clinical Neuropsychology*. New York: Oxford University Press; 1985.
- Heilman KM, Van Den Abell T. Right hemisphere dominance for attention: the mechanism underlying hemispheric asymmetries of inattention (neglect). *Neurology*. 1980; 30(3):327–330. [PubMed: 7189037]
- Heilman KM, Watson RT, Bower D, Valenstein E. Right hemisphere dominance for attention. *Rev Neurol (Paris)*. 1983; 139(1):15–17. [PubMed: 6407086]
- Hickok G. Functional anatomy of speech perception and speech production: psycholinguistic implications. *J Psycholinguist Res*. 2001; 30(3):225–235. [PubMed: 11523272]
- Hickok G, Poeppel D. Towards a functional neuroanatomy of speech perception. *Trends Cogn Sci*. 2000; 4(4):131–138. [PubMed: 10740277]
- Hickok G, Poeppel D. The cortical organization of speech processing. *Nat Rev Neurosci*. 2007; 8(5):393–402. [PubMed: 17431404]
- Jenkinson M, Smith S. A global optimisation method for robust affine registration of brain images. *Med Image Anal*. 2001; 5(2):143–156. [PubMed: 11516708]
- Karnath HO, Ferber S, Himmelbach M. Spatial awareness is a function of the temporal not the posterior parietal lobe. *Nature*. 2001; 411(6840):950–953. [PubMed: 11418859]
- Lacquaniti F, Guigon E, Bianchi L, Ferraina S, Caminiti R. Representing spatial information for limb movement: role of area 5 in the monkey. *Cereb Cortex*. 1995; 5(5):391–409. [PubMed: 8547787]
- Lehmann M, Crutch SJ, Ridgway GR, Ridha BH, Barnes J, Warrington EK, et al. Cortical thickness and voxel-based morphometry in posterior cortical atrophy and typical Alzheimer's disease. *Neurobiol Aging*. 2009
- Ludwig, E.; Klingler, J. *Atlas Cerebri Humani* The inner structure of the brain demonstrated on the basis of macroscopical preparations. Boston: Little, Brown; 1956.
- Makris, N. Dissertation. Dept of Behavioral Neuroscience, Boston University; Boston, MA: 1999. Delineation of human association fiber pathways using histologic and magnetic resonance methodologies. <http://www.cma.mgh.harvard.edu/staff/nm/Makris-PhD-THESIS.pdf>

- Makris N, Biederman J, Valera EM, Bush G, Kaiser J, Kennedy DN, et al. Cortical thinning of the attention and executive function networks in adults with attention-deficit/hyperactivity disorder. *Cereb Cortex*. 2007a; 17(6):1364–1375. [PubMed: 16920883]
- Makris N, Kennedy DN, McInerney S, Sorensen AG, Wang R, Caviness VS Jr, et al. Segmentation of subcomponents within the superior longitudinal fascicle in humans: a quantitative, in vivo, DT-MRI study. *Cereb Cortex*. 2005; 15(6):854–869. [PubMed: 15590909]
- Makris N, Meyer JW, Bates JF, Yeterian EH, Kennedy DN, Caviness VS. MRI-Based topographic parcellation of human cerebral white matter and nuclei II. Rationale and applications with systematics of cerebral connectivity. *Neuroimage*. 1999; 9(1):18–45. [PubMed: 9918726]
- Makris N, Pandya DN. The extreme capsule in humans and rethinking of the language circuitry. *Brain Struct Funct*. 2009; 213(3):343–358. [PubMed: 19104833]
- Makris N, Pandya DN, Normandin JJ. Quantitative DT-MRI investigations of the human cingulum bundle. *Central Nervous System Spectrums*. 2002; 7(7):522–528.
- Makris N, Papadimitriou GM, Kaiser JR, Sorg S, Kennedy DN, Pandya DN. Delineation of the middle longitudinal fascicle in humans: a quantitative, in vivo, DT-MRI study. *Cereb Cortex*. 2009; 19(4):777–785. [PubMed: 18669591]
- Makris N, Papadimitriou GM, Sorg S, Kennedy DN, Caviness VS, Pandya DN. The occipitofrontal fascicle in humans: a quantitative, in vivo, DT-MRI study. *Neuroimage*. 2007b; 37(4):1100–1111. [PubMed: 17681797]
- Makris N, Preti MG, Asami T, Pelavin P, Campbell B, Papadimitriou GM, et al. Human middle longitudinal fascicle: variations in patterns of anatomical connections. *Brain Struct Funct*. 2012
- Makris N, Seidman LJ, Ahern T, Kennedy DN, Caviness VS, Tsuang MT, et al. White matter volume abnormalities and associations with symptomatology in schizophrenia. *Psychiatry Res*. 2010; 183(1):21–29. [PubMed: 20538438]
- Malcolm JG, Shenton ME, Rathi Y. Filtered multitensor tractography. *IEEE Trans Med Imaging*. 2010; 29(9):1664–1675. [PubMed: 20805043]
- Menjot de Champfleury N, Lima Maldonado I, Moritz-Gasser S, Machi P, Le Bars E, Bonafe A, et al. Middle longitudinal fasciculus delineation within language pathways: A diffusion tensor imaging study in human. *Eur J Radiol*. 2013; 82(1):151–157. [PubMed: 23084876]
- Mesulam MM. Large-scale neurocognitive networks and distributed processing for attention, language, and memory. *Ann Neurol*. 1990; 28(5):597–613. [PubMed: 2260847]
- Mesulam MM. From sensation to cognition. *Brain*. 1998; 121(Pt 6):1013–1052. [PubMed: 9648540]
- Molholm S, Sehatpour P, Mehta AD, Shpaner M, Gomez-Ramirez M, Ortigue S, et al. Audio-visual multisensory integration in superior parietal lobule revealed by human intracranial recordings. *J Neurophysiol*. 2006; 96(2):721–729. [PubMed: 16687619]
- Mountcastle VB, Lynch JC, Georgopoulos A, Sakata H, Acuna C. Posterior parietal association cortex of the monkey: command functions for operations within extrapersonal space. *J Neurophysiol*. 1975; 38(4):871–908. [PubMed: 808592]
- Poremba A, Saunders RC, Crane AM, Cook M, Sokoloff L, Mishkin M. Functional mapping of the primate auditory system. *Science*. 2003; 299(5606):568–572. [PubMed: 12543977]
- Posner MI, Petersen SE. The attention system of the human brain. *Annu Rev Neurosci*. 1990; 13:25–42. [PubMed: 2183676]
- Rajarethinam R, Sahni S, Rosenberg DR, Keshavan MS. Reduced superior temporal gyrus volume in young offspring of patients with schizophrenia. *Am J Psychiatry*. 2004; 161(6):1121–1124. [PubMed: 15169705]
- Rathi Y, Malcolm JG, Bouix S, Westin C-F, Shenton ME. False Positive Detection using Filtered Tractography. International Society For Magnetic Resonance in Medicine Scientific Meeting (ISMRM). 2010
- Rilling JK, Glasser MF, Preuss TM, Ma X, Zhao T, Hu X, et al. The evolution of the arcuate fasciculus revealed with comparative DTI. *Nat Neurosci*. 2008; 11(4):426–428. [PubMed: 18344993]
- Rohrer JD, Warren JD, Omar R, Mead S, Beck J, Revesz T, et al. Parietal lobe deficits in frontotemporal lobar degeneration caused by a mutation in the progranulin gene. *Arch Neurol*. 2008; 65(4):506–513. [PubMed: 18413474]

- Sakata H, Takaoka Y, Kawarasaki A, Shibutani H. Somatosensory properties of neurons in the superior parietal cortex (area 5) of the rhesus monkey. *Brain Res.* 1973; 64:85–102. [PubMed: 4360893]
- Sapolsky D, Bakkour A, Negreira A, Nalipinski P, Weintraub S, Mesulam MM, et al. Cortical neuroanatomic correlates of symptom severity in primary progressive aphasia. *Neurology.* 2010; 75(4):358–366. [PubMed: 20660866]
- Saur D, Kreher BW, Schnell S, Kummerer D, Kellmeyer P, Vry MS, et al. Ventral and dorsal pathways for language. *Proc Natl Acad Sci U S A.* 2008; 105(46):18035–18040. [PubMed: 19004769]
- Schmahmann, JD.; Pandya, DN. *Fiber Pathways of the Brain.* New York: Oxford University Press; 2006.
- Schmahmann JD, Pandya DN, Wang R, Dai G, D'Arceuil HE, de Crespigny AJ, et al. Association fibre pathways of the brain: parallel observations from diffusion spectrum imaging and autoradiography. *Brain.* 2007; 130(Pt 3):630–653. [PubMed: 17293361]
- Seeley WW, Crawford RK, Zhou J, Miller BL, Greicius MD. Neurodegenerative diseases target large-scale human brain networks. *Neuron.* 2009; 62(1):42–52. [PubMed: 19376066]
- Seltzer B, Pandya DN. Afferent cortical connections and architectonics of the superior temporal sulcus and surrounding cortex in the rhesus monkey. *Brain Res.* 1978; 149(1):1–24. [PubMed: 418850]
- Seltzer B, Pandya DN. Further observations on parieto-temporal connections in the rhesus monkey. *Exp Brain Res.* 1984; 55(2):301–312. [PubMed: 6745368]
- Seltzer B, Pandya DN. Post-rolandic cortical projections of the superior temporal sulcus in the rhesus monkey. *J Comp Neurol.* 1991; 312(4):625–640. [PubMed: 1761745]
- Song SK, Sun SW, Ju WK, Lin SJ, Cross AH, Neufeld AH. Diffusion tensor imaging detects and differentiates axon and myelin degeneration in mouse optic nerve after retinal ischemia. *Neuroimage.* 2003; 20(3):1714–1722. [PubMed: 14642481]
- Song SK, Sun SW, Ramsbottom MJ, Chang C, Russell J, Cross AH. Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. *Neuroimage.* 2002; 17(3):1429–1436. [PubMed: 12414282]
- Suchan J, Umarova R, Schnell S, Himmelbach M, Weiller C, Karnath HO, et al. Fiber pathways connecting cortical areas relevant for spatial orienting and exploration. *Hum Brain Mapp.* 2013
- Talairach, J.; Tournoux, P. *Co-Planar Stereotaxic Atlas of the Human Brain.* New York: Thieme Medical Publishers, Inc; 1988.
- Thiebaut de Schotten M, Dell'Acqua F, Forkel SJ, Simmons A, Vergani F, Murphy DG, et al. A lateralized brain network for visuospatial attention. *Nat Neurosci.* 2011; 14(10):1245–1246. [PubMed: 21926985]
- Tuch DS, Reese TG, Wiegell MR, Makris N, Belliveau JW, Wedeen VJ. High angular resolution diffusion imaging reveals intravoxel white matter fiber heterogeneity. *Magn Reson Med.* 2002; 48(4):577–582. [PubMed: 12353272]
- Turken AU, Dronkers NF. The neural architecture of the language comprehension network: converging evidence from lesion and connectivity analyses. *Front Syst Neurosci.* 2011; 5:1. [PubMed: 21347218]
- Wang Y, Fernandez-Miranda JC, Verstynen T, Pathak S, Schneider W, Yeh FC. Rethinking the Role of the Middle Longitudinal Fascicle in Language and Auditory Pathways. *Cereb Cortex.* 2012
- Wedeen VJ, Wang RP, Schmahmann JD, Benner T, Tseng WY, Dai G, et al. Diffusion spectrum magnetic resonance imaging (DSI) tractography of crossing fibers. *Neuroimage.* 2008; 41(4):1267–1277. [PubMed: 18495497]
- Yeh FC, Tseng WY. NTU-90: a high angular resolution brain atlas constructed by q-space diffeomorphic reconstruction. *Neuroimage.* 2011; 58(1):91–99. [PubMed: 21704171]

Figure 1.

Method of tractography of the two major MdLF subcomponents, i.e., the superior temporal-angular, or STG(MdLF)AG, connection and the superior temporal-superior parietal, or STG(MdLF)SPL, connection. The regions of waypoints used for the tractographic delineation of STG(MdLF)AG (yellow) and STG(MdLF)SPL (cyan) are shown in (a) frontal and (b) lateral 3D views in a representative subject. The regions used to delineate STG(MdLF)AG include the cortex of the superior temporal gyrus and temporal pole (temporal region), the cortex of angular gyrus (AG), and a white matter STG ROI; for STG(MdLF)SPL, regions include the cortex of the superior temporal gyrus and temporal pole (temporal region), the cortex of superior parietal lobule (SPL) and a white matter STG ROI. The latter is located at a coronal level corresponding to $Y = -13$ mm in the rostrocaudal dimension of the Talairach coordinate system (Talairach and Tournoux 1988) as elaborated upon in more detail in Methods. The delineation of the white matter (WM) superior temporal gyrus (STG) ROI for both hemispheres is shown (red) in (c). The 3D Slicer software environment was used to generate these images. “STG” in the terms

“STG(MdLF)AG” and “STG(MdLF)SPL” refers to the cortices of the superior temporal gyrus and dorsal temporal pole as also described in Methods. Abbreviations: AG = angular gyrus; L = left; MdLF = middle longitudinal fascicle; R = right; ROI = region of interest; SPL = superior parietal lobule; STG = superior temporal gyrus; STG(MdLF)AG = superior temporal-angular connection of MdLF; STG(MdLF)SPL = superior temporal-superior parietal connection of MdLF; TP = temporal pole; WM = white matter.

Figure 2.

Results of MdLF tractography showing STG(MdLF)AG (yellow) and STG(MdLF)SPL (cyan) as the two major subcomponents of the MdLF. Penetration of STG(MdLF)AG and STG(MdLF)SPL fibers in the dorsal temporopolar cortex is clearly visible bilaterally. A frontal view is shown in (a), a right lateral view in (b), and a left lateral view in (c). The 3D Slicer software environment was used to generate these images. Abbreviations: A = anterior; AG = angular gyrus; L = left; MdLF = middle longitudinal fascicle; P = posterior; R = right; ROI = region of interest; SPL = superior parietal lobule; STG = superior temporal gyrus; STG(MdLF)AG = superior temporal-angular connection of MdLF; STG(MdLF)SPL = superior temporal-superior parietal connection of MdLF; TP = temporal pole; WM = white matter.

Figure 3.

Delineation of the superior temporal-angular (STG(MdLF)AG) (light green) and the superior temporal-superior parietal (STG(MdLF)SPL) (dark green) connections of the MdLF and their differentiation from other long association fiber tracts in the human cerebrum. The 3D Slicer software environment was used to generate these images. Abbreviations: AF = arcuate fascicle; AG = angular gyrus; CB = cingulum bundle; EmC/IFOF = extreme capsule/inferior frontooccipital fascicle; ILF = inferior longitudinal fascicle; STG(MdLF)AG = superior temporal-angular connection of MdLF; STG(MdLF)SPL = superior temporal-superior parietal connection of MdLF; SFOF = superior frontooccipital fascicle; SLF I, II, III = superior longitudinal fascicle I, II, III; SPL = superior parietal lobule; UF = uncinate fascicle.

Figure 4.

Probability maps of STG(MdLF)AG and STG(MdLF)SPL. The probability maps of STG(MdLF)AG (red) and STG(MdLF)SPL (blue) are shown in sagittal, coronal, and axial views. The maps were obtained by averaging tract masks generated from the fiber tracts of all subjects previously registered to the MNI152 standard space. Probability maps are shown in color code and thresholded at a value of probability equal to 0.008. The 3D Slicer software environment was used to generate these images. In (a), the STG(MdLF)AG and STG(MdLF)SPL are shown on the right hemisphere in a series of three parasagittal sections the location of which is indicated in the axials contained within the smaller rectangular areas. In (b), three coronal sections (upper row) are cross-referenced with three axial sections (bottom row) showing the location of STG(MdLF)AG and STG(MdLF)SPL in the dorsal TP (left coronal), STG (middle coronal) and lateral parietal lobe (including AG and SPL). STG(MdLF)AG maintains a ventrolateral position in relation to STG(MdLF)SPL, which is located dorsomedially. In (c), STG(MdLF)AG (upper panel) and STG(MdLF)SPL (lower panel) are shown separately in a series of four coronal plates in the rostrocaudal dimension from left to right. These sections in both the upper and lower panels, are at the level of the dorsal TP (left coronal), STG (second coronal from left), temporoparietal transition region (third coronal from left) and lateral parietal lobe (rightmost coronal, including AG and SPL). The position of the four coronal sections is indicated in the sagittal section as 1, 2, 3 and 4 in the rostrocaudal dimension. Abbreviations: A = anterior; AG = angular gyrus; inpars = intraparietal sulcus; L = left; MdLF = middle longitudinal fascicle; STG(MdLF)AG = superior temporal-angular connection of MdLF; P = posterior; R = right; STG = superior temporal gyrus; SPL = superior parietal lobule; STG(MdLF)SPL = superior temporal-superior parietal connection of MdLF; TP = temporal pole.

Figure 5.

3D Visualization of the STG(MdLF)AG (red) and STG(MdLF)SPL (blue) probability maps described in Figure 4. 3D visualization of the probability maps were done using 3D Slicer environment. In (a), the probability maps of both STG(MdLF)AG and STG(MdLF)SPL combined are shown in ventral, dorsal, frontal, caudal and lateral views. In (b), STG(MdLF)AG and STG(MdLF)SPL are shown magnified against the background of a coronal and an axial MRI section, which are intersecting each other, to emphasize their relative location within the anatomical context of the superior temporal region (including the temporal pole and superior temporal gyrus) and the parietal lobe. Instead, in (c) and (d), STG(MdLF)AG and STG(MdLF)SPL are shown individually to appreciate their absolute anatomical locations with more clarity. Panels (e), (f) and (g) are identical to (a), (b) and (c) respectively, the only difference being that the anatomical background created by the two MRI sections has been removed to emphasize the two fiber tracts individually, and to depict

with more clarity their relative locations and size. STG(MdLF)AG is positioned in a ventrolateral location with respect to STG(MdLF)SPL, which is located dorsomedially. Abbreviations: A = anterior; AG = angular gyrus; inpars = intraparietal sulcus; L = left; MdLF = middle longitudinal fascicle; STG(MdLF)AG = superior temporal-angular connection of MdLF; P = posterior; R= right; STG = superior temporal gyrus; SPL = superior parietal lobule; STG(MdLF)SPL = superior temporal-superior parietal connection of MdLF; TP = temporal pole.

Figure 6.

In this figure, the complete trajectories of the two major subdivisions of the middle longitudinal fascicle (MdLF) of all subjects have been placed in the Talairach coordinate space. In (a), the STG(MdLF)AG (red) and STG(MdLF)SPL (blue) are shown in 3-D against the background of a lower T1-weighted axial slice intersected by a posterior coronal section. In (b), the STG(MdLF)AG and STG(MdLF)SPL are visualized in transparency, whereas within their core are shown their “center-lines”. A center-line, which represents the average shape of fiber tracts, has been created by concatenating average center-points across all coronal sections in which a fiber tract is present. In (c), the STG(MdLF)AG (red) and STG(MdLF)SPL (blue) are represented by their center-lines extending from the temporal pole (TP) to the angular gyrus (AG) and superior parietal lobule (SPL) respectively. The trajectories of the STG(MdLF)AG and STG(MdLF)SPL are depicted in the Talairach coordinate space in axial (d), right sagittal (e) and left sagittal (f) views. The complete Talairach coordinates of their center-points are reported in detail in the APPENDIX. Abbreviations: AG = angular gyrus; inpars = intraparietal sulcus; L = left; MdLF = middle longitudinal fascicle; STG(MdLF)AG = superior temporal-angular connection of MdLF; R = right; SPL = superior parietal lobule; STG(MdLF)SPL = superior temporal-superior parietal connection of MdLF; TP = temporal pole.

Figure 7.

Comparison of single-tensor and multi-tensor tractography models Two types of tractography have been performed to define the middle longitudinal fascicle (MdLF) trajectory on the same diffusion data (same subject). Yellow virtual fibers (on a, b and d), have been created using single-tensor tractography to represent MdLF as described in our previous publication (N. Makris et al. 2012). Red and blue virtual fibers (c and d) illustrate the two major subdivisions of MdLF, namely STG(MdLF)AG (red) and STG(MdLF)SPL (blue) obtained using multi-tensor tractography. The latter method offers several advantages over single-tensor tractography, such as less fiber truncations shown in the enlarged “box” in (b), and more virtual fibers and more connections indicated by arrows in (c). In (d) the single-tensor and multi-tensor tractography results for MdLF are superimposed. Abbreviations: MdLF = middle longitudinal fascicle; STG(MdLF)AG = superior temporal-angular connection of MdLF; STG(MdLF)SPL = superior temporal-superior parietal connection of MdLF.

Table 1

Measures of volume, fractional anisotropy, axial diffusivity, radial diffusivity, and length of the left and right STG(MdLF)AG, STG(MdLF)SPL and MdLF (i.e., STG(MdLF)AG and STG(MdLF)SPL combined) in 74 healthy human subjects. Symmetry index of these parameters is also reported herein.

STG(MdLF)AG	Volume (cm ³)			FA *			AD			RD			Length (mm)		
	Left	Right	SI	Left	Right	SI	Left	Right	SI	Left	Right	SI	Left	Right	SI
Mean	2.11	2.43	-0.140	344.37	337.84	0.019	1148.64	1136.45	0.011	643.62	644.80	-0.002	87.20	84.50	0.031
SD	1.73	2.21	-0.243	40.02	32.07	0.221	76.96	74.89	0.027	95.84	73.76	0.260	10.03	10.13	-0.010
STG(MdLF)SPL	Left	Right	SI	Left	Right	SI	Left	Right	SI	Left	Right	SI	Left	Right	SI
Mean	1.68	2.39	-0.345	374.59	373.12	0.004	1152.09	1136.95	0.013	612.21	607.27	0.008	100.57	102.10	-0.015
SD	1.36	2.33	-0.528	43.14	55.14	-0.244	93.19	67.30	0.323	106.96	115.33	-0.075	10.89	9.53	0.133
MdLF	Left	Right	SI	Left	Right	SI	Left	Right	SI	Left	Right	SI	Left	Right	SI
Mean	3.79	4.81	-0.237	358.02	354.95	0.009	1150.20	1136.69	0.012	629.44	626.60	0.005	93.24	93.04	0.002
SD	1.58	2.26	-0.354	43.96	47.98	-0.087	84.39	71.05	0.172	105.38	102.96	0.023	12.35	13.20	-0.066

Abbreviations: AD = axial diffusivity; FA = fractional anisotropy; MdLF = middle longitudinal fascicle; RD = radial diffusivity; SD = standard deviation; SI = symmetry index; STG(MdLF)AG = superior temporal-angular connection of MdLF; STG(MdLF)SPL = superior temporal-superior parietal connection of MdLF.

* FA range has been rescaled from 0 – 1 to 0 – 1000.