ORIGINAL ARTICLE

Asymmetry, connectivity, and segmentation of the arcuate fascicle in the human brain

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Received: 2 September 2013/Accepted: 4 March 2014 © Springer-Verlag Berlin Heidelberg 2014

Abstract The structure and function of the arcuate fascicle is still controversial. The goal of this study was to investigate the asymmetry, connectivity, and segmentation patterns of the arcuate fascicle. We employed diffusion spectrum imaging reconstructed by generalized q-sampling and we applied both a subject-specific approach (10 subjects) and a template approach (q-space diffeomorphic reconstruction of 30 subjects). We complemented our imaging investigation with fiber microdissection of five post-mortem human brains. Our results confirmed the highly leftward asymmetry of the arcuate fascicle. In the template, the left arcuate had a volume twice as large as the right one, and the left superior temporal gyrus provided five times more volume of fibers than its counterpart. We identified four cortical frontal areas of termination: pars opercularis, pars triangularis, ventral precentral gyrus, and caudal middle frontal gyrus. We found clear asymmetry of the frontal terminations at pars opercularis and ventral precentral gyrus. The analysis of patterns of connectivity revealed the existence of a strong structural segmentation

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T. Verstynen · F.-C. Yeh Department of Bioengineering, Carnegie Mellon University, Pittsburgh, PA, USA in the left arcuate, but not in the right one. The left arcuate fascicle is formed by an *inner or ventral pathway*, which interconnects pars opercularis with superior and rostral middle temporal gyri; and an *outer or dorsal pathway*, which interconnects ventral precentral and caudal middle frontal gyri with caudal middle and inferior temporal gyri. The fiber microdissection results provided further support to our tractography studies. We propose the existence of *primary and supplementary language pathways* within the dominant arcuate fascicle with potentially distinct functional and lesional features.

Keywords Arcuate fascicle · Diffusion spectrum imaging · Tractography · Language · Fiber dissection

Abbreviations

AAL	Automated anatomical labeling
AF	Arcuate fascicle
BA	Brodmann area
CORID	Committee for oversight research involving dead
DSI	Diffusion spectrum imaging
DTI	Diffusion tensor imaging
EPI	Echo planar imaging
fMRI	Functional MRI
FoV	Field of view
GQI	Generalized q-sampling imaging
ITG	Inferior temporal gyrus
MdLF	Middle longitudinal fascicle
MTG	Middle temporal gyrus
ODF	Orientation distribution function
QA	Quantitative anisotropy
ROI	Region of interest
SLF	Superior longitudinal fascicle
STG	Superior temporal gyrus
TR	Repetition time

Introduction

The arcuate fascicle (AF) is a white matter fiber tract that links lateral temporal cortex with frontal cortex via a dorsal projection that arches around the Sylvian fissure (Türe et al. 2000; Schmahmann et al. 2007; Fernandez-Miranda et al. 2008b). Classical anatomical and clinical studies (Dick and Tremblay 2012) revealed its general trajectory along with the superior longitudinal fascicle (SLF) and described the role of the left AF/SLF in language function. More recent anatomical studies using post-mortem fiber microdissection techniques have proposed the differentiation of the AF as a fronto-temporal tract and the SLF as a fronto-parietal tract (Fernandez-Miranda et al. 2008b), and provided further detail regarding the cortical termination of their fibers (Martino et al. 2013b).

Modern autoradiography studies in monkeys, have suggested that the AF does not link the posterior-superior temporal gyrus (Wernicke's area) with the posterior inferior frontal gyrus (Broca's area), thus supporting the view that the left AF is not a language-related tract (Schmahmann and Pandya 2006). Although these "in vivo" tracttracing studies are considered the "gold standard" in connectional Neuroanatomy (Schmahmann et al. 2007), the translation of their results from non-human primates to humans is problematic, especially for language-related tracts (Catani et al. 2005).

In the last decade, diffusion tensor imaging (DTI) studies have revealed the significant leftward asymmetry and cortical terminations of the AF providing new insights into the connectivity of the AF and its assumed major functional role in language processing (Catani et al. 2005; Hagmann et al. 2006; Powell et al. 2006; Vernooij et al. 2007). However, DTI-based tractography has several technical limitations, such as inability to map fiber endings of white matter before contacting the cortical mantle, failure to solve fiber crossings and to follow bundles within fiber tracts, and excessive false fiber continuity generating pseudotracts (Catani et al. 2005; Glasser and Rilling 2008; Dick and Tremblay 2012; Wang et al. 2013). As a consequence, the connectivity pattern of the AF is still controversial and warrants further investigation. In particular, Dick and Tremblay (2012) debated: the existence of direct posterior temporal-inferior frontal connectivity (Broca-Wernicke); the specific location of the rostral (frontal) terminations of the AF; and the extension of the caudal (temporal) component of the AF. Individual differences in the anatomy of the AF and SLF have also contributed to the uncertain delineation of their fiber pathway connectivity.

The goal of this study was to investigate in healthy subjects the asymmetry, connectivity and segmentation patterns of the left and right AF. In order to overcome some of the limitations of DTI studies, here we employ diffusion spectrum imaging (DSI) (Wedeen et al. 2005) reconstructed by generalized q-sampling imaging (GQI) (Yeh et al. 2010) as a high angular resolution based approach that leverages high directional sampling of diffusion imaging space to get better resolution of underlying white matter geometry for tractography. This approach has shown to provide accurate replication of complex known neuroanatomical features where DTI failed (Fernandez-Miranda et al. 2012; Yeh et al. 2013), and has facilitated innovative studies on the structural connectivity of several fiber tracts such as the middle longitudinal fascicle (MdLF) (Wang et al. 2013), the cortico-spinal tract (Verstynen et al. 2011), the corpus callosum (Jarbo et al. 2012), dorsal stream visual pathways (Greenberg et al. 2012), and the cortico-striatal pathways (Verstynen et al. 2011). Here we have applied both a subject-specific approach and a template approach, and in an attempt to cross-validate the "in vivo" fiber tracking results, we have complemented our imaging investigation with fiber microdissection techniques of the left and right AF in post-mortem human brains.

Materials and methods

Participants

Ten neurologically healthy adults (7 male; all right-handed; age range 21–36) from the local University of Pittsburgh community took part in this experiment, conducted as part of a larger data collection effort. All participants were prescreened prior to scanning to rule out any contraindications to MRI. The internal review board at the University of Pittsburgh approved all the procedures used here and written consent was obtained from all participants prior to testing.

In addition to subject-specific analysis, we also conducted fiber tracking on a high angular resolution brain template reflecting an average of 30 adult brains. For this, twenty male and ten female subjects were recruited from the local Pittsburgh community and the Army Research Laboratory in Aberdeen, Maryland. All subjects were neurologically healthy, with no history of either head trauma or neurological or psychiatric illness. Subject ages ranged from 21 to 45 years of age at the time of scanning and four were left handed (2 male, 2 female).

Image acquisition and reconstruction

DSI data for the subject-specific approach were acquired on 3T Tim Trio System (Siemens) using a 32-channel coil. This involved a 43-min. 257-direction scan using a twicerefocused spin-echo EPI sequence and multiple q values (TR = 9,916 ms, TE = 157 ms, voxel size = $2.4 \times 2.4 \times$ 2.4 mm, FoV = 231×231 mm, $b_{\text{max}} = 7,000$ s/mm²). For anatomical comparisons, we also included high resolution anatomical imaging, employing a 9-min T1-weighted axial MPRAGE sequence (TR = 2,110 ms, TE = 2.63 ms, flip angle = 8° , 176 slices, FoV = $256 \times 256 \text{ mm}^2$, voxel size = $0.5 \times 0.5 \times 1.0 \text{ mm}^3$). DSI data were reconstructed using a GQI approach. The orientation distribution functions (ODFs) were reconstructed to 362 discrete sampling directions and a diffusion distance ratio of 1.2, as used in the original GQI description (Yeh et al. 2010). Briefly, ODF is a probabilistic density function on the two-dimensional surface of a sphere. The ODF can be calculated from diffusion MRI signals, and the local maximums in an ODF are often regarded as the axonal fiber orientations in deterministic fiber tracking, a method that calculates the axonal trajectories between cortical areas. Diffusion spectrum imaging (DSI) is a diffusion MRI q-space imaging method that acquires diffusion signals with multiple b-values to calculate average propagator and the diffusion ODF. The diffusion encoding sampling scheme of DSI is arranged as grids points in the q-space and distinguishes itself from the common-used shell arrangement that is limited to single diffusion gradient strength. The multiple diffusion gradient strength design gives DSI better coverage on both fast and slow diffusion (Yeh et al. 2013).

DSI template

For the high angular resolution brain template, thirty participants were scanned on a Siemens Verio 3T system in the Scientific Imaging and Brain Research Center at Carnegie Mellon University using a 32-channel head coil. We collected a 50 min, 257-direction DSI scan using a twicerefocused spin-echo EPI sequence and multiple q values (TR = 9,916 ms, TE = 157 ms, voxel size = $2.4 \times 2.4 \times$ 2.4 mm, FoV = 231×231 mm, $b_{max} = 5,000$ s/mm², 51 slices). Head movement was minimized during the image acquisition through padding supports and all subjects were confirmed to have minimal head movement (<1 voxel shift) during the scan prior to inclusion in the template.

All images were processed using a q-space diffeomorphic reconstruction method described previously (Yeh and Tseng 2011). Briefly, this approach uses a non-linear coregistration approach (ICBM-152 space template regularization, 16 non-linear iterations) that registers the voxel-coordinate into MNI space while also maintaining distortion of the q-space vector during the normalization process. From here orientation distribution functions (ODFs) are reconstructed to spatial resolution of 2 mm³. The final template image was created using the spin distribution functions obtained from q-space

diffeomorphic reconstruction across all 30 subjects, and the resulting template can be used to obtain the representative tractography of the subject population. The white matter surface is rendered independently from an externally supplied $1 \times 1 \times 1$ mm resolution ICBM-152 white matter image (Fonov et al. 2011).

Fiber tracking and analysis

Diffusion fiber tracking was conducted using a multiple fiber version of the streamline tracking algorithm (Basser et al. 2000; Yeh et al. 2010). The fiber tracts were generated by whole brain seeding, and the tracts passing the region of interest (ROI) were selected for analysis. In voxels with multiple fiber orientations, fiber tracking was initiated separately for each orientation, and fiber progression continued with a step size of 1.0 mm, minimum fiber length of 20 mm, and turning angle threshold of 60°. If multiple fiber orientations exist in the current progression location, the fiber orientation that is nearest to the incoming direction and forms a turning angle smaller than 60° is selected to determine the next moving direction. To smooth each track, the next moving directional estimate of each voxel was weighted by 20 % of the previous incoming direction and 80 % of the nearest fiber orientation. This progression repeated until the quantitative anisotropy (QA) (Yeh et al. 2010) of the fiber orientation dropped below a preset threshold (0.03-0.06 depending on the subject) or there was no fiber selected within the 60° angular range in the progression. The OA termination threshold was adjusted on a per subject basis depending on the relative signal to noise of each scan. Since the smoothing parameter may affect the tracking result, and the optimal value can be different for different tracking targets, we conducted a preliminary study to determine the smoothing parameter used in our study, which is described in the following. We fixed other tracking parameters and used the same regions of interests in fiber tracking (as stated previously). Different smoothing parameters (80, 60, 40, 20 %, and no smoothing) were applied to generate 10,000 fiber tracks for each parameter. The qualitative comparison was conducted by inspecting the fiber trajectories, and the optimal parameter was selected by the results that offered the tractography with less false fibers, including premature termination, false turning, and false connection.

FreeSurfer (http://surfer.nmr.mgh.harvard.edu) was used to segment cortical gyral ROIs using each participant's T1weighted MPRAGE image (Desikan et al. 2006). For the template, ICBM-152 T1 template image (Fonov et al. 2011) was segmented in FreeSurfer. The ROIs for tract selection were assigned automatically by using the cortical parcellation obtained from anatomical segmentation. For reconstruction of the right and left AFs, we employed three



Fig. 1 Reconstruction of the arcuate fascicle using three seed regions (*STG* superior temporal gyrus, *MTG* middle temporal gyrus, *ITG* inferior temporal gyrus) and one region-of-interest (ROI) located at the level of the post-central gyrus bilaterally. **a** Posterior-superior

view, **b** lateral view; FreeSurfer cortical parcellation is used to determine the cortical termination of the fibers (*Pars Operc.* pars opercularis)

 Table 1
 Asymmetry of the arcuate fascicle

Volume ml (%)	L	R	L-STG	R-STG	L-MTG	R-MTG	L-ITG	R-ITG	Lateral index
1	35.28 (73)	12.94 (27)	7.66 (16)	2.67 (6)	13.28 (27)	4.84 (10)	14.34 (30)	5.43 (11)	1.00
2	36.25 (78)	9.97 (22)	7.05 (15)	_	14.12 (31)	6.95 (15)	15.08 (32)	3.02 (07)	1.15
3	35.06 (57)	26.43 (43)	8.25 (13)	3.82 (6)	15.61 (25)	14.98 (24)	11.2 (19)	7.63 (13)	0.28
4	29.53 (61)	19.26 (39)	10.67 (22)	4.59 (9)	9.47 (19)	9.14 (19)	9.39 (20)	5.53 (11)	0.42
5	19.24 (50)	19.01 (50)	3.47 (09)	-	5.14 (13)	9.19 (24)	10.63 (28)	9.82 (26)	0.01
6	38.98 (66)	19.99 (34)	7.01 (12)	3.18 (5)	17.16 (29)	7.59 (13)	14.81 (25)	9.22 (16)	0.64
7	32.44 (61)	21.07 (39)	13.15 (25)	4.24 (8)	9.13 (17)	5.92 (11)	10.16 (19)	10.91 (20)	0.42
8	51.5 (56)	41.12 (44)	12.46 (13)	10.51 (11)	20.59 (22)	19.59 (21)	18.45 (21)	11.02 (12)	0.21
9	33.58 (75)	11.42 (25)	11.39 (25)	-	10.81 (24)	8.74 (19)	11.38 (26)	2.68 (6)	0.98
10	33.62 (73)	12.51 (27)	13.76 (30)	1.33 (3)	10.62 (23)	8.28 (18)	9.24 (20)	2.9 (6)	0.91
Total	34.54 (65)	19.38 (35)	9.48 (18)	3.03 (4.8)	12.4 (23)	9.38(17.4)	12.8 (24)	6.9 (12.8)	0.56
Template	39.23 (67)	18.70 (33)	6.37 (11)	1.15 (2)	18.53 (32)	13.32 (23)	13.90 (24)	4.63 (8)	0.70

The tract (and subtract) volumes are accounted by the number of voxels occupied by the fiber trajectories (streamlines) and are reported in milliliters (ml). The figures in parentheses represent the relative volume of each tract and subtract in percentage (%) considering that left and right AF together represent 100 % of the volume. The lateralization index is calculated based on the volume of left and right AF (see "Materials and methods"). *STG* superior temporal gyrus, *MTG* middle temporal gyrus, *ITG* inferior temporal gyrus, *Lateral* lateralization

cortical ROIs bilaterally acting as the seeding regions: superior temporal gyrus (STG), middle temporal gyrus (MTG), and inferior temporal gyrus (IFG) (Fig. 1). To simplify the analysis of the connectivity of the AF, we assumed that the AF fibers only originated from STG, MTG, and ITG (as defined by the Automated Anatomical Labeling; this labeling system provides larger ROIs that were viewed as ideal for generating tracts). An ROI mask was drawn on the coronal plane at the level of the postcentral gyrus. This was used to select only the fibers that pass from STG, MTG, and ITG to the frontal region bilaterally. In order to quantify and compare left and right AF, and the contribution of each seeding region, we calculated the volume of streamlines by accounting the number of voxels occupied by the fiber trajectories (streamlines). We also calculated the relative volume of streamlines providing the percentage of volume for left and right AF, and for each seeding region (Table 1). Recent reviews in diffusion fiber tracking (Jones and Cercignani 2010; Jbabdi and Johansen-Berg 2011; Jones et al. 2013) are against using the number of streamlines to derive a quantitative index due to poor reproducibility, and therefore we preferred the volume of streamlines as a more reliable measure. We also calculated the lateralization index (modified from Catani et al. 2007) based on the formula:

 $[(Left AF volume - Right AF volume)/(Left AF volume + Right AF volume)] \times 2$

This formula was also applied to calculate the lateralization index for subtracts of the left and right AF. Based on Catani et al. (2007), positive values of the index indicate a greater volume of streamlines in the left AF compared with the right, and viceversa; values around the zero indicate a similar volume between left and right; positive values greater than 0.4 indicate left lateralization, with extreme left lateralization when the index is equal or greater than 1.

In order to determine the cortical terminations of the AF in the frontal region we imported the cortical frontal areas from two different atlases: the Talairach Atlas, which provides Brodmann areas, and FreeSurfer cortical parcellation (Desikan et al. 2006), which is more accurate and has less overlapping than the AAL system.

The segmentation of the AF was conducted by performing fiber tracking using each temporal and frontal cortical area of origin/termination as seeding point, and registering the cortical connectivity for that particular seed region. The segments of the AF were also quantitatively analyzed by calculating the occupying volume of the fiber tracts. The diffusion fiber tracking and the analysis were performed by DSI Studio (http://dsi-studio.labsolver.org).

Fiber dissection technique

Five normal brains (age 32–81, 3 females) were obtained at routine autopsy. The study was approved by CORID at University of Pittsburgh. The specimens were fixed in a 10 % formalin aqueous solution for at least 4 weeks and then they were subsequently frozen for 2 additional weeks at -16 °C, according to the method introduced by (Ludwig and Klingler 1965; Agrawal et al. 2011) and used in multiple studies before (Türe et al. 2000; Fernandez-Miranda et al. 2008a, b, 2012). Progressive dissection of the white matter tracts was performed by peeling off the gray matter and isolating the fiber bundles in their glial sheets. We undertook the fiber dissection studies at the Surgical Neuroanatomy Lab (University of Pittsburgh) with the aid of microsurgical instrumentation and surgical microscope (6 to 40 magnification, Carl Zeiss, OPMI CS-NC).

Results

Asymmetry of the AF: left and right comparison

The results of our *subject-specific* fiber tractography study confirmed that the AF is clearly leftward asymmetric. In order to complete this comparison we reconstructed at the same time the left and right AF on each subject (Fig. 1). Then, we compared the left-right ratio based on the volume of the left and right AF. Considering all 10 subjects together, the average left AF represented 65 % (50–78 %) of the total mean volume, and the right AF just 35 % (22–50 %). In 9 out of 10 subjects, the left AF was larger than the right AF, with the remaining subject having similar volume for left and right AF. The lateralization index showed that there were two cases with no lateralization, six cases with left lateralization, and two cases of extreme left lateralization (Table 1).

We also studied the volume contributions of each seed region (STG, MTG, ITG) bilaterally. The STG contributed 18 % (9–30 %) of the mean volume to the left AF and just 4.8 % (0–11 %) to the right AF, with an extreme left lateralization index of 1.03. The MTG provided 23 % (13–31 %) to the left AF and 17.4 % (10–24 %) to the right AF, with a lateralization index of 0.27. The ITG originated 24 % (19–32 %) of the volume of fibers to the left AF and 12.8 % (6–26 %) to the right AF, with a left lateralization index of 0.6 (Table 1). These results show the pronounced leftward asymmetric contributions of the STG, the mild leftward asymmetry of fibers from ITG, and symmetrical distribution of fibers from MTG.

The 30-subject *template* approach showed similar results. The left AF had a volume twice as large as the right AF (67 vs. 33 %), with a lateralization index of 0.7. Considering the volume contribution of each gyrus, we found that the left STG provided 5 times more volume of fibers than the right STG (extreme left lateralization index of 1.39); the difference in the contribution of the left and right MTG was much less pronounced, with a 1.5 ratio in favor of the left side (lateralization index of 0.32); the left ITG provided 3 times more volume to the AF than the right AF (lateralization index of 1.0) (Table 1; Fig. 2).

Connectivity of the AF

We identified four different cortical areas of termination of the AF fibers in the frontal region: pars opercularis, pars triangularis, precentral gyrus (ventral portion), and middle frontal gyrus (caudal portion) (Fig. 3). Fibers of the AF terminated at pars opercularis in all 10 subjects on the left side, and only in 3 out of 10 subjects on the right side. Fibers were converging at pars triangularis in 3 out of 10 subjects on the left side and 5 out of 10 in the right side. The ventral precentral gyrus was a site of termination of AF fibers in 8 out of 10 subjects on the left side but only in 2 out of 10 subjects on the right side. Fibers of the AF terminated at the caudal middle frontal gyrus in all subjects, bilaterally. These results show clear asymmetry of the frontal terminations of the AF at pars opercularis and precentral gyrus, but not at pars triangularis or middle frontal gyrus (Table 2).

Fig. 2 Asymmetry of the AF: right and left comparison in the 30-subject template. **a**, **b** Right and left AF, respectively (RGB coding). c, d Right and left AF; streamlines originating from the superior temporal gyrus (STG) are colored *red*, those from the middle temporal gyrus (MTG) are green, and those from inferior temporal gyrus (ITG) are *blue*. **e**, **f** The T1 sagittal MRI slice has been superimposed to illustrate the trajectory of the right and left AF



The study of the 30-subject template showed quite similar results. We identified four different cortical areas of termination of the left AF fibers in the frontal region: pars opercularis (dorsal and ventral portions), pars triangularis (dorsal portion, at the junction with pars opercularis), precentral gyrus (ventral portion), and middle frontal gyrus (caudal portion) (Fig. 3a-d). Based on the parcellation with Brodmann areas, the fibers were terminating at BA45 (pars triangularis), BA44 (pars opercularis), BA6 (ventral precentral and caudal middle frontal gyri), and BA9 (dorsolateral prefrontal cortex) (Fig. 4). On the right side, the AF fibers terminated at only three cortical frontal areas: pars triangularis (ventral portion; BA45), pars opercularis (dorsal portion only, corresponding to BA9 in Talairach Atlas), and middle frontal gyrus (caudal portion; BA6) (Fig. 3e, f). We also analyzed the volume contributions of each frontal cortical area to the AF volume bilaterally (and their lateralization indexes) to found that there is an

extreme asymmetry of the cortical connections to the ventral precentral gyrus (BA6) and pars triangularis (dorsal; BA45), and mild left lateralization for the caudal middle frontal region (BA6–BA9). When analyzing the contribution of pars opercularis we noted no significant asymmetry between connectivity of left and right dorsal portions of pars opercularis (BA9), but extreme left lateralization for ventral portion of pars opercularis (BA44) (Table 3).

Segmentation of the AF

Our *subject-specific approach* of AF connectivity revealed a clear segmentation, in particular in the left AF. In order to find common patterns of connectivity within the AF, we studied the structural interconnectivity between temporal gyri and frontal regions. Importantly, we observed that both in left and right hemispheres the connectivity of MTG



Fig. 3 Cortical areas of termination of the AF fibers in the frontal region. **a** Lateral view of the cortical surface of the left hemisphere prior to start fiber dissection. **b** Lateral view, fiber microdissection of the left AF showing clear termination fibers at the precentral gyrus and pars opercularis. **c** Free surfer cortical segmentation and fiber tractography reconstruction of the left AF in the 30-subject template; to correlate with **a**. **d** There are four different cortical areas of termination, and the fibers terminating at each area have been colored accordingly: precentral gyrus (*green*), middle frontal gyrus (MFG; *blue*), pars opercularis (*red*), pars triangularis (*yellow*); to correlate

and ITG differed clearly for the rostral versus dorsal portions of the gyri. Therefore, we analyzed rostral and caudal MTG-ITG separately. Interestingly, the caudal portion of

with **b**. **e** Lateral view, fiber microdissection of the right AF with termination fibers at the MFG gyrus and dorsal portion of pars opercularis. **f** Fiber tractography reconstruction of the right AF in the 30-subject template. There are three different cortical areas of termination, and the fibers terminating at each area have been colored accordingly: middle frontal gyrus (*blue*), dorsal portion of pars opercularis (*green*), and pars triangularis (*red*); to correlate with **e**. Note the different pattern of frontal termination of the AF fibers at the left (**d**) and right (**f**) hemispheres

the MTG-ITG corresponds with BA37, while the rostral portion correlates with BA21 (MTG) and BA20 (ITG). This resulted in a 4 by 4 matrix with distinct connectivity

Arcuate fascicle ($N = 10$ /template)	Pars opercularis	Ventral precentral	Caudal middle frontal	Dorsal pars triangularis
STG	BLBLLLLLB/L	L0L000L0L/L	0000L0000L/0	BL0B00000R/R
Rostral MTG	LLBLLLLLL/B	000L0LLL0L/L	000LLLLL0L/0	L0R000000/B
Caudal MTG	L0R0L00000/0	LBLL0LLLRL/L	RBLBBBBBBB/B	00R00R0000/0
ITG	0LL0000000/0	LL0L0LLL0L/0	BBBBBBBBBBB/B	0LR00R0000/L

Table 2 Connectivity of the arcuate fascicle in 10 individual subjects and 30-subjects template

L connection present in the left hemisphere, R connection present in the right hemisphere, B connection present bilaterally, 0 no connection

features for left and right AFs (Table 2). The strongest pattern of connectivity for both left and right AF (no asymmetry), present in most subjects, was between the caudal middle frontal gyrus (BA6 and BA9) and caudal MTG-ITG (BA37). Additionally, in all subjects the left AF displayed consistent interconnectivity between pars opercularis (BA44) on the frontal region and STG (BA22 and BA42) and rostral MTG (BA21) on the temporal side. This pattern of connectivity was present in only a few subjects on the right side. We also found another strong pattern of connectivity of the left AF between the precentral gyrus (BA6) and caudal MTG-ITG (BA37). This was present in 8 out of 10 subjects on the left side, but only in 2 subjects on the right side (Table 2). The analysis of these patterns of connectivity revealed the existence of a clear structural segmentation in the left AF, but not in the right AF. The left AF can be described as formed by an inner or ventral pathway, which interconnects pars opercularis (BA44) with STG (BA22-BA42) and rostral MTG (BA21), and an outer or dorsal pathway, which interconnects ventral precentral (BA6) and caudal middle frontal gyrus (BA6 and BA9) with caudal MTG-ITG (BA37).

The study of the 30-subject template confirmed a consistent pattern of segmentation within the left AF (Fig. 5): the posterior STG (posterior BA22) and planum temporale (BA42) connect only with pars opercularis (BA44) and ventral precentral gyrus (BA6), whereas pars opercularis (BA44) connects only with posterior STG (posterior BA22) and rostral MTG (BA21) (Fig. 5a). This corresponds with what we called the inner or ventral pathway (Fig. 6). The ventral precentral gyrus (BA6) and MTG (BA21 and BA37) (Fig. 5b, c), the caudal middle frontal gyrus (BA6 and BA8) and caudal MTG-ITG (BA37) (Fig. 5d), and the dorsal pars triangularis/dorso-lateral prefrontal cortex (BA45-BA9) and rostral MTG and ITG (BA21 and BA20) (Fig. 5e, f) are strongly interconnected, respectively. These correlate with the outer or dorsal pathway (Fig. 6). Interestingly, there is one frontal area, ventral precentral gyrus (BA6), and one temporal region, MTG (BA21), which are part of both the inner (ventral) and outer (dorsal) pathways (Table 2).

In addition to this characteristic segmentation, the left AF displays a ventral-rostral and dorsal-caudal

organization, where more ventral frontal regions interconnect with more rostral temporal areas, and more dorsal frontal regions connect with more caudal temporal areas. The length of the fibers appears to increase as they get deeper: the shorter interconnection between STG and pars opercularis is more superficial than the longer fibers interconnecting ventral precentral gyrus with MTG. The latter fibers are located more superficially than the fibers interconnecting caudal middle frontal gyrus and pars triangularis with caudal and rostral MTG, respectively.

The right AF also presents a segmentation pattern that follows the principle of ventral-rostral and dorsal-caudal organization as described for the left AF, but in a more simplistic way. The STG (BA22) only connects with the ventral pars triangularis (BA45), forming the equivalent to the inner or ventral pathway. The outer or dorsal pathway is formed by fibers connecting the dorsal pars opercularis (BA9) with rostral MTG-ITG (BA21–BA20), and caudal middle frontal gyrus (BA6) with caudal MTG-ITG (BA37).

The comparison between left and right AFs revealed that the shape of the fascicle, in particular the angle formed by the arching fibers between the temporal and frontal regions is less than 90° for the left side (10/10 subjects and template), and is usually larger than 90° for the right AF (7/10 subjects and template). This is easily explained by the much stronger inner pathway of the left AF when compared to the right one (Fig. 2).

Fiber dissection of the AF

Microdissection was started at the lateral surface of the brain with the left and right AF being dissected separately. By removing the short U-fibers that cover the temporal, parietal, and frontal regions, we exposed the underlying AF and followed the fibers from the temporal gyri (STG, MTG, ITG) to the frontal region. The fibers connecting the temporal region with the inferior parietal lobule (supra-marginal and angular gyri) were dissected; these fibers form the vertical or indirect segment of the AF (Catani et al. 2005; Schmahmann et al. 2007; Fernandez-Miranda et al. 2008a, b; Martino et al. 2013a), and were not the subject of our investigation. Similarly, the fibers from the inferior parietal lobule to the frontal region (Schmahmann



Fig. 4 Subtracts of the left AF based on frontal areas of origin/termination. a, b Pars opercularis, c, d precentral gyrus, e, f middle temporal gyrus, g, h pars triangularis

et al. 2007; Fernandez-Miranda et al. 2008b) representing the SLF were carefully dissected as they were not the focus of our research. In the left hemisphere, the main temporal bundle of the AF showed the first frontal termination of the fibers at the ventral precentral gyrus. This group of fibers was mainly

Table 3 Volume contributions of each frontal cortical area to the AF volume bilaterally in the 30-subject template

Template	Pars opercularis	Pars triangularis	Ventral precentral	Caudal middle frontal
Left	13 % (ventral and dorsal)	21 % (dorsal)	21 %	21 %
Right	10 % (dorsal)	2 % (ventral)	0 %	12 %
Lateralization index	0.26	1.65	2	0.54

The figures in parenthesis represent the relative volume contribution in percentage (%) of each frontal area considering that left and right AF together represent 100 % of the volume

arising from STG and MTG. After removal of the fibers connecting with the ventral precentral gyrus, we could follow the fibers to their end regions more rostrally, mainly related to the caudal middle frontal gyrus and pars opercularis. Further dissection in successive left hemispheres showed that the fibers that reached pars opercularis were interconnected with the STG, rostral part of MTG, and adjacent superior temporal sulcus, while the fibers reaching the caudal middle frontal gyrus were mainly coming from the caudal part of MTG and ITG (Fig. 7).

In right hemispheres, the AF exhibited remarkable differences compared to the left AF. The right AF was mainly comprised of fibers interconnecting the caudal part of MTG with the caudal middle frontal gyrus. The typical group of fibers running from the STG and rostral MTG to pars opercularis and ventral precentral gyrus was not found in the right hemispheres. These main differences between left and right AFs, confirmed our tractography data.

Discussion

Our study of the left and right AF connectivity in 10 healthy subjects and a template of 30 individuals, supports previous studies demonstrating the highly leftward AF asymmetry (Galaburda et al. 1978; Nucifora et al. 2005; Glasser and Rilling 2008; Thiebaut de Schotten et al. 2012; Catani et al. 2007) and provides further details of its distribution in the left and right hemispheres. This asymmetry, which is present in the majority of subjects, has been mainly attributed to the language left-sided lateralization. However, a DTI and fMRI study of the AF indicated that its leftward structural asymmetry is not correlated with handedness or functional language lateralization (Vernooij et al. 2007). A fetal study indicated that the asymmetric development of the AF is "pre-programmed" (Chi et al. 1977), and is probably due to a decrease of fiber density in the right hemisphere (Galaburda et al. 1978).

Our results confirm the findings of Glasser and Rilling (2008) describing that the AF terminations at the STG are highly left dominant. We could not confirm this left predominance for the MTG subtract, as in our subjects the volume of MTG terminations (predominantly the rostral part) was approximately equal between hemispheres. ITG contribution was predominantly leftwardly. We have also concluded that the extension of the AF towards the anterior and middle segments of the STG, documented by previous DTI (Catani et al. 2005; Anwander et al. 2007) and microdissection studies (Catani et al. 2005; Martino et al. 2013b) including ours (Fernandez-Miranda et al. 2008b) truly represents a false continuation artifact; we recently provided evidence that this artifact is secondary to the apposition of the MdLF and the AF at the temporo-parietal junction (Wang et al. 2013). Regarding the asymmetry of the frontal terminations of the AF, we show that ventral pars opercularis (BA44), ventral precentral gyrus (BA6), and pars triangularis (BA45) are strongly interconnected with temporal regions in the left hemisphere but not in the right one.

According to the dual stream model of language processing, a dorsal stream interfaces auditory-phonological information with the motor system and supports functions such as aspects of speech production and phonological short-term memory-the prototype task is speech repetition; and a ventral stream interfaces auditory-phonological information with the conceptual system and therefore supports comprehension-the prototype task is listening to meaningful speech (Hickok and Poeppel 2007; Hickok 2012). The neuroanatomical substrates of the dual model of auditory language processing are controversial. Some investigators maintain that AF and SLF represent the dorsal pathway primarily involved in phonology and syntax, and extreme capsule (Saur et al. 2008; Weiller et al. 2011; Hickok 2012) and/or uncinate fasciculus (Friederici 2006, 2009) represent the ventral pathway involved in semantics. Glasser and Rilling (2008) based on a correlative DTI and task-based fMRI study, suggested the division of AF into two subtracts, a ventral pathway terminating at the posterior STG (connecting the BA22 to BAs 44 and 6) and a dorsal pathway terminating at the MTG (connecting BAs 21 and 37 to BAs 44, 45, 6 and 9), both strongly left lateralized. The authors concluded that STG terminations are overlapped with phonological activations, whereas MTG terminations are overlapped with lexical-semantic activations. Thus, functionally the AF might contribute to both the dorsal and ventral pathways of language processing, although anatomically is dorsally located. In this report we have meticulously analyzed the connectivity pattern of the AF to conclude that the proposed ventral/ dorsal subtracts certainly helps to understand the structural layout of interconnections within the left AF. Our inner



Fig. 5 Pattern of segmentation within the left AF. **a** The posterior STG (posterior BA22) and planum temporale (BA42) connect only with pars opercularis (BA44) and ventral precentral gyrus (BA6) (*red* subtract), whereas pars opercularis (BA44) connects only with posterior STG (posterior BA22) and rostral MTG (BA21) (*orange* subtract). **b** The ventral precentral gyrus (BA6) connects with MTG (BA21 and BA37) (*light green* subtract). **c**, **d** The caudal middle frontal gyrus (BA6 and BA8) and caudal MTG-ITG are

interconnected; fibers arising from the MTG are colored *green* and fibers arising from caudal middle frontal gyrus are colored *light blue*. **e**, **f** The dorsal pars triangularis/dorso-lateral prefrontal cortex (BA45–BA9) and rostral MTG and ITG (BA21 and BA20) are interconnected; fibers arising from ITG are colored *dark blue*, and fibers from pars triangularis are *yellow*. Please note there is overlapping of fibers (and colors) in interconnected regions

pathway, corresponding to Glasser and Rilling' *ventral subtract*, interconnects STG (BA22–BA42) and rostral MTG (BA21) with pars opercularis (BA44) and most ventral premotor cortex (BA6). The *outer pathway*, corresponding to Glaser and Rilling' *dorsal subtract*, interconnects caudal MTG-ITG (BA37) and ITG (BA20) with ventral precentral (BA6) and caudal middle frontal gyrus (BA6 and BA9). We prefer to divide the AF into "outer" and "inner" subtracts instead of dorsal and ventral subtracts to avoid the confusion of the ventral AF subtract with the ventrally located language tracts. In analogy with other functional domains such as the visual or motor systems, we suggest that the inner pathway interconnects "primary" language areas (Broca's and Wernicke's), whereas the outer pathway interconnects "supplementary" language areas. Therefore, we propose the existence of *primary and supplementary language pathways* within the AF with potentially distinct functional and lesional features. In both visual and motor systems, the supplementary areas (BA18 and BA19 for visual system, BA6 for motor) are located



Fig. 6 a Fiber tractography, b fiber dissection, c schematic illustration. The *inner or ventral pathway* (*red*) interconnects pars opercularis (BA44) and most ventral portion of precentral gyrus (BA6) with STG (BA22) and rostral MTG (BA21), and corresponds to the primary language pathway. The *outer or dorsal pathway* (*green*) interconnects ventral precentral gyrus (BA6), caudal middle frontal gyrus (BA6 and BA8), and dorsal pars triangularis/dorsal prefrontal cortex (BA45 and BA9) with MTG and ITG (BA21–BA20–BA37), and correlates with the supplementary language pathway

adjacent to the primary areas (BA17 for visual system, BA4 for motor). Similarly in the language system, the supplementary language areas (dorso-lateral prefrontal cortex, BA9; ventral premotor cortex, BA6; dorsal pars triangularis, BA45/9; caudal MTG-ITG, BA37; ITG, BA20) are surrounding the primary language areas. The primary language pathway is then related to linear encoding and articulation (Broca's area) and speech recognition or phonologic decoding of heard speech (Wernicke's area). The supplementary pathway would be implicated in word selection (dorso-lateral prefrontal cortex, BA9), semantic aspects of language processing (pars triangularis, BA45) (Amunts et al. 2004), and lexical-semantic processing (BA21, BA20, BA37) (Vandenberghe et al. 1996; Hickok and Poeppel 2004). Injury to the primary language pathway would cause more traditional Broca's or Wernicke's aphasia syndromes and its variants, and damage to the supplementary language pathway would cause word finding difficulties, anomias, and semantic paraphasias. From clinical point of view, dysfunctions of the supplementary language network are more frequently encountered, simply because its size is significantly larger than the primary language network and therefore more susceptible to damage by brain lesions. Similarly, large hemispheric lesions such as middle cerebral artery strokes would cause damage to both pathways. The proposed subdivision of the AF would complement structurally and functionally the ventral language pathways.

In a recent review of the fiber tracts related to the language system, Dick and Tremblay (Dick and Tremblay 2012) summarized several points of controversy in relation to the AF, such as its frontal and temporal sites of origin/ termination and the existence of a direct connection between Broca's and Wernicke's areas. We believe the results of our study bring significant information that provides further support to previous DTI studies by Catani et al. (2005) and Glasser and Rilling (2008). The differences in the AF structure in monkeys based on autoradiography studies and in humans based on DTI have been recently analyzed by Rilling et al. (2008, 2011) and attributed to strong modifications of the AF during human evolution. Our study indicates that in the human brain, the AF has evolved to extensively interconnect primary and supplementary language-related areas in the frontal and temporal lobes.

In the right hemisphere, only the MTG pathway is well represented and functional MRI studies connected it with prosodic processing (Riecker et al. 2012; Glasser and Rilling 2008). The possible contribution of right AF to speech recognition is supported by fMRI and lesion data (Hickok and Poeppel 2007). Importantly, Catani et al. (2007) showed that individuals with more symmetric patterns of connections are better overall at remembering words using semantic association, and paradoxically, they stated that bilateral representation, not extreme lateralization, might ultimately be advantageous for specific cognitive functions.

From the methodological point of view, the DSI variant we used in this report involves a dense sampling of angular space for underlying water diffusion (Wedeen et al. 2008). This significantly improves our ability to reconstruct complex fiber crossings and partial volume effect that typically impairs DTI tractography (Fernandez-Miranda 2013). By integrating DSI with improved reconstruction and deterministic tractography approaches (Yeh et al.



Fig. 7 Stepwise fiber dissection of the left AF. The fibers are followed from the temporal gyri (STG, MTG, ITG) to the frontal region revealing a characteristic segmentation compatible with the fiber tractography findings

2010) we can acquire significantly better resolution of otherwise difficult to map fiber pathways that can be followed from one cortical region to adjacent or distant cortical (and subcortical) areas through complex crossings, providing direct evidence of cortical site of origin or termination of the fibers without need for estimation or approximation (Yeh et al. 2010; Verstynen et al. 2011; Fernandez-Miranda et al. 2012). In addition, here we have analyzed both individual subjects, which allows for studying variability in the connectivity patterns, and a 30-subject template, which provides information on average connectivity patterns. The results of both approaches are, for the most part, similar and compatible, with the exception of the marked difference on the connectivity between the rostral MTG and the dorsal pars triangularis. Only two of the 10 subjects show this connection, yet it is present bilaterally in the template. We believe this discrepancy is related to the averaging that leads to smoothing in the spatial domain when dealing with a template.

Our results are complemented by fiber microdissection of post-mortem human brains, a technique that was used by the early pioneers in human white matter anatomy to describe most fiber pathways in the human brain (Türe et al. 2000; Agrawal et al. 2011; Ludwig and Klingler 1965). Although lacking histological precision, fiber microdissection techniques are currently used to provide novel information on the anatomy of the fiber tracts at the macroscopic level (Martino et al. 2013b). The combined application of fiber microdissection and advanced fiber tracking techniques for the study of human white matter anatomy aids in proper interpretation and analysis of results (Fernandez-Miranda et al. 2012; Wang et al. 2013). The two methods of cross validation used here increase confidence that the results are not artifacts of one method and provide stronger support for the described connectivity of the studied tract than either method alone.

Limitations of this study

The results presented here have several limitations. First, the advanced fiber tracking technique we employed has multiple advantages over DTI but still suffers several methodological limitations. When analyzing the AF, we found false continuation of fibers at the frontal region with the external capsule fibers; this false continuation of fibers was eliminated in the segmentation process by using cortical areas of origin/termination but their mere presence indicates the possibility of losing some fibers because these temporal fibers could not be followed to their frontal termination. For this reason we can state that our tractography findings show clear evidence of certain patterns of connectivity (absence of false positive connections) but there could be more interconnecting fibers not well reconstructed with our technique (potential false negative connections). We believe this represents a minority of fibers, but still should be taken in consideration. It is also important to note that our volume calculation only accounted the number of voxels passed by the fiber trajectories and that different subparts of AF may coexist in the same voxels, leading to error in volume estimation. A solution to this problem is acquiring images with higher spatial resolution to minimize the error.

Second, the cortical segmentation process might involve minor misalignment and overlapping in between adjacent cortical ROIs, which would cause misidentification of the cortical site of origin/termination of fibers. As a consequence, we acknowledge that our results might contain a small spatial error, that otherwise does not change the general conclusions of the study. More importantly, there are multiple cortical labeling systems, which add confusion and difficulty to the analysis of cortical connectivity. In our study, we employed three different atlases (see "Materials and methods") aiming to offer a more complete assessment of structural connectivity. However, the interpretation of the results based on three different sources might result in cortical labeling discrepancies.

Third, fiber connections within the AF are known to be reciprocal but we cannot ascertain this based on fiber tracking or dissection studies. Here we use the term origin or termination of fibers indistinctly, being aware of the relativity of this assumption. Similarly, we have employed structural techniques that cannot offer any functional information, and consequently any assigned function to the fiber pathways is just based on the role of the interconnected cortical regions as obtained from functional studies.

Finally, we have excluded from this study adjacent fiber tracts that are intimately and spatially related to the AF, which are needed to fully understand the AF-related language network. These are the superior longitudinal fascicle and its segments (fronto-parietal connections) (Makris et al. 2005), the vertical component of the AF (temporoparietal connections) (Catani et al. 2005; Martino et al. 2013a), and the short U-fibers in between adjacent gyri, which are beyond the scope of this study.

Conclusion

The connectivity pattern of the left and right AFs presented here was first studied in 10 subjects, and then confirmed analyzing a DSI template of 30 subjects. The template approach does not allow for studying the individual differences as the subject-specific approach, but by averaging the data of a large sample it does provide unique information on the average connectivity patterns, and in this particular case, the average pattern of the left and right AFs. Importantly, both our subject-specific and template approaches show the dominance of the left AF and its characteristic structural arrangement in primary and supplementary pathways connecting specific frontal and temporal cortical areas.

Acknowledgments The first author would like to acknowledge Maria Jose, Blanca, Martin, Sol, and Alonso for their continuous support to complete this project. The Copeland Fund of The Pittsburgh Foundation.

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