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Horizontal portion of arcuate fasciculus fibers track to pars opercularis, not pars triangularis, in right and left hemispheres: A DTI study

Elina Kaplan [a], Margaret A. Naeser [a,*], Paula I. Martin [a], Michael Ho [a], Yunyan Wang [a], Errol Baker [a], Alvaro Pascual-Leone [b,c]

[a] Veterans Affairs Boston Healthcare System and the Harold Goodglass Boston University Aphasia Research Center, Department of Neurology, Boston University School of Medicine, USA
[b] Berenson-Allen Center for Noninvasive Brain Stimulation, Beth Israel Deaconess Medical Center, Harvard Medical School, USA
[c] Institut Universitari de Neurorehabilitació Guttmann-UAB, Badalona 08916, Spain

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ABSTRACT

The arcuate fasciculus (AF) is a white matter pathway traditionally considered to connect left Broca's area with posterior language zones. We utilized diffusion tensor imaging (DTI) in eight healthy subjects (5 M) to track pathways in the horizontal mid-portion of the AF (hAF) to subregions of Broca's area — pars triangularis (PTr) and pars opercularis (POp); and to ventral premotor cortex (vPMC) in the right and left hemispheres (RH, LH). These pathways have previously been studied in the LH, but not in the RH. Only 1/8 subjects showed fiber tracts between PTr and hAF in the RH (also, only 1/8 in the LH). In contrast to PTr, 5/8 subjects showed fiber tracts between POp and hAF in the RH (8/8 in the LH). Fiber tracts for vPMC were similar to those of POp, where 7/8 subjects showed fiber tracts between vPMC and hAF in the RH (8/8 in the LH). Our designated hAF could have included some of the superior longitudinal fasciculus (SLF) III, because it is difficult to separate the two fiber bundles. The SLF III has been previously reported to connect supramarginal gyrus with POp and vPMC in the LH. Thus, although the present DTI study showed almost no pathways between PTr and hAF in the RH (and in the LH), robust pathways were observed between POp and/or vPMC with hAF in the RH (and in LH). These results replicate previous studies for the LH, but are new, for the RH. They could contribute to better understanding of recovery in aphasia.

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Introduction

The anatomy and function of the left (L) posterior inferior frontal gyrus has been studied since the time of Broca, (1861). Broca's area is critically involved in language, including syntactic, semantic and phonological processing (Price, 2000; Bookheimer, 2002; Grodzinsky and Amunts, 2006 for review; Saur et al., 2008). In some functional imaging studies involving healthy subjects, the L pars triangularis (PTr) portion of Broca's area has been observed to activate in semantic processing, whereas the L pars opercularis (POp), relatively more in phonological processing (Buckner et al., 1995; Price et al., 1996; Fiez, 1997; Poldrack et al., 1999; Gold and Buckner, 2002; Devlin et al., 2003; Nixon et al., 2004). Lesion in L Broca's area continues to be associated with speech disturbance (Mohr et al., 1978; Alexander et al., 1990). Lesion deep to Broca's area including periventricular white matter is associated with longer-lasting nonfluent aphasia (Naeser et al., 1989).

The contribution of right (R) Broca's homologue to language includes prosody, discourse and processing of syntactic violations (Blumstein et al., 1977; Ross, 1981; Yeni-Komshian and Lafontaine, 1983; Bradvik et al., 1991; Buckner et al., 1995; Nichelli et al., 1995; Winner et al., 1998; Meyer et al., 2000; Finger et al., 2003; Nishitani et al., 2005 for review). A role for the R POp and R ventral premotor cortex (vPMC) in promoting recovery of speech in nonfluent aphasia has been suggested since 1877 when Barlow reported his detailed anatomical study (Barlow, 1877). A 10 year-old boy lost speech for only 10 days following a first stroke restricted to L POp and L vPMC. One month later, however, a second stroke occurred, located in the same, right hemisphere (RH) homologous areas (R POp and R vPMC). Following the second stroke, he lost all speech again, and there was "loss of voluntary motor power over the muscles concerned in articulation and the first part of deglutition." The boy died two months later, without any recovery of speech. See Fig. 1. More recently, a PET study by Blank et al. (2003) has supported a role for the R POp in aphasia recovery in patients with L frontal lesion. They observed that the R POp "contributed to processes involved in the assembly of the sound structure of speech" in these patients.

In addition, repetitive transcranial magnetic stimulation (rTMS) studies with nonfluent aphasia patients have observed that suppression of R POp can impair naming in some patients (Naeser et al., 2002, 2005b). Surprisingly, however, suppression of R PTr for 20 min a day (10 days) improves naming in these same patients (lasting 2–

* Corresponding author. Aphasia Research Center (12-A), V.A. Boston Healthcare System, JP, 150 So. Huntington Ave., Boston, MA 02130, USA. Fax: +1 617 739 8926.
E-mail address: mnaeser@bu.edu (M.A. Naeser).

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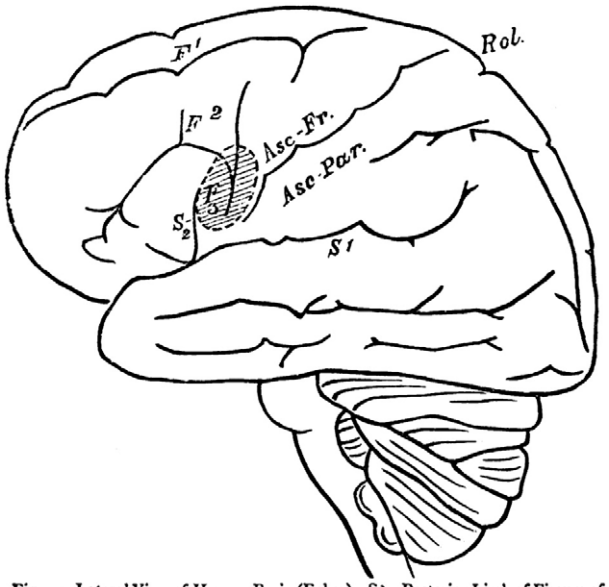

Fig. 1.—Lateral View of Human Brain (Ecker). S_1. Posterior Limb of Fissure of Sylvius. S_2. Anterior Limb of Fissure of Sylvius. Rol. Fissure of Rolando. Asc. Fr. Ascending Frontal Convolution. Asc. Par. Ascending Parietal Convolution. F_1, F_2, F_3. Superior Middle and Inferior Frontal Convolutions. The dotted portion represents the situation of the lesion on each side of the brain—viz., in the lower end of the ascending frontal and the hinder end of the middle and inferior frontal convolutions.

Fig. 1. Aphasia case reported by Barlow (1877) showing detailed drawing of lesion in POp and vPMC following initial L hemisphere stroke. The second stroke (a few months later) occurred in identical areas in the RH; there was no recovery of speech. The L and R PTr remained intact, suggesting possibly different roles for POp and PTr in aphasia recovery. Permission obtained from The British Medical Journal, for July 28, 1877, page 104.

8 months post-rTMS treatments) (Naeser et al., 2005a,b; Martin et al., 2009; Naeser et al., 2010; Hamilton et al., 2010). Thus, the two parts of R Broca's homologue (PTr and POp) may play different roles in aphasia recovery that remain to be clarified.

The relevance of the L arcuate fasciculus (AF) in aphasia syndromes has been summarized by Geschwind (1965), and recently reviewed in historical context by Catani and Mesulam (2008). Dejerine (1895) considered the arcuate fasciculus (AF) to be part of a larger pathway, the superior longitudinal fasciculus (SLF). The AF/SLF is traditionally believed to be a system of fibers connecting frontal lobe with the parietal and temporal lobes. The horizontal portion of the AF (hAF) runs parallel to SLF II and SLF III (Petrides and Pandya, 1984; Makris et al., 2005; Glasser and Rilling, 2008).

The MRI technology of diffusion tensor imaging (DTI) is based on examining the directional dependence of water diffusion throughout the brain (Moseley et al., 1990; Beaulieu, 2002) and permits visualization of white matter fiber tracts *in vivo*. Several DTI studies have confirmed white matter pathways between L Broca's area and posterior language zones (via the AF/SLF), including superior or middle temporal gyrus and the supramarginal gyrus (Catani et al., 2005; Parker et al., 2005; Powell et al., 2006; Frey et al., 2008; Saur et al., 2008). Saur et al. (2008) observed separate (dorsal and ventral) white matter pathways from POp and PTr to posterior language zones in the LH. The major pathway from ventrolateral premotor cortices (including POp) followed a more dorsal route via the AF/SLF to supramarginal gyrus (SMG) and superior temporal lobe; a pathway believed to be important for sensory-motor mapping of sound to articulation. Hickok and Poeppel (2004, 2007) have proposed the dorsal stream to be LH dominant, and critical for auditory–motor integration. The major pathway from ventrolateral prefrontal cortex (including PTr) followed a ventral route via extreme capsule, to middle temporal lobe; this pathway is believed to be important for linguistic processing of sound to meaning. Other DTI studies have observed pathways between L ventral premotor cortex (vPMC) and the supramarginal gyrus (Croxson et al., 2005; Makris et al., 2005; Rushworth et al., 2006).

As reviewed above, pathways between the AF and parts of Broca's area, and the vPMC, have previously been examined in the LH, but not in the RH. The primary purpose of the present study was to utilize DTI to examine pathways between the horizontal mid-portion of the AF (hAF) and parts of Broca's area (PTr, POp), and vPMC in the RH in healthy control subjects. These pathways were also examined in the LH. This study was undertaken as a first step, and reference point for future clinical studies (Mori et al., 2002). In aphasia patients, knowledge of pathways between the AF/SLF and inferior frontal areas in the RH could contribute to a better understanding of recovery in aphasia.

Materials and methods

Participants

Eight healthy subjects participated in the study (ages 55–71, 5 M). All subjects were native speakers of English, right-handed, with no history of neurological or psychiatric disease. Demographics are presented in Supplemental Table 1. Each subject provided signed, informed consent for this research as approved by each institution.

A 3-Tesla whole body scanner (Intera, Philips; Boston University Center for Biomedical Imaging) was used to acquire structural and diffusion-weighted imaging. A 3D SPGR series of structural images was acquired for each subject.

Structural image acquisition

For half of the subjects (N1–N4), the following parameters were used to acquire the structural images: TR = 9.9 ms; TE = 4.6 ms; matrix size 256 × 256; FOV 256; slice thickness = 1 mm. For half of the subjects (N5–N8), who were scanned at a later date, the parameters were: TR = 6.85 ms, TE = 3.2 ms, matrix size 256 × 256, FOV 256, slice thickness = 1.20 mm. All the participants' images were acquired in the sagittal view and re-sliced into the axial plane.

Diffusion-weighted image acquisition

For subjects N1–N4, the acquisition parameters for diffusion-weighted images (DWI) were as follows: TR = 10,686 ms; TE = 84 ms; matrix size 128 × 128, FOV 256, fat suppression, number of slices = 44, slice thickness = 3.00 mm, $b = 1000$ s/mm^2, 15 directions, gradient strength and SENSE (sensitivity encoding) reduction factor = 2.00. For subjects N5–N8, the acquisition parameters for DWI were as follows: TR = 10686 ms, TE = 91 ms, matrix size 128 × 128, FOV 230, fat suppression, number of slices = 73, slice thickness = 2.00 mm, $b = 1000$ s/mm^2, 15 directions, gradient strength and SENSE (sensitivity encoding) reduction factor = 2.00. Although the scans were acquired at different times, the slice thickness for all subjects fell within typical DTI parameters (1–5 mm) (Mori and van Zijl, 2002).

For each subject, three DWI data sets were acquired in 15 directions. These were corrected for motion, co-registered and averaged within and between acquisitions using Philips averaging software (Philips Medical Systems). Structural images were co-registered to DTI images in SPM99 (http://www.fil.ion.ucl.ac.uk/spm/) using mutual information.

Fiber tracking parameters

Diffusion tensors, fractional anisotropy (FA), and fiber tracts were calculated using Diffusion Toolkit software (Wang et al., 2007) that uses a deterministic tractography algorithm based on the FACT tractography algorithm (Mori and van Zijl, 2002). Fibers were

generated across the entire brain with the following parameters: Mask 1: b0 field map, lower threshold of 120 and upper threshold of 3000, angle threshold 40, Invert Y; Mask 2: FA map, lower threshold 150 and upper threshold 900. The masks and thresholds were utilized to remove the background and "non-trackable" areas in the brain.

First, the b0 field map was used to segment grey and white matter, then the FA map was overlaid to constrain data within the white matter. A threshold of 0.15 was set in Diffusion Toolkit (Wang et al., 2007) so that tracts were terminated if the FA dropped below this threshold (Mori and van Zijl, 2002).

Fiber tracking analyses

Tractography data were obtained using TrackVis, an interactive program for fiber tracking reconstruction, display and analysis (Wang et al., 2007). This software permitted the use of hand-drawn selected regions of interest (ROIs). The white matter pathways were studied between one ROI (beginning seedpoint) and a second ROI (target seedpoint).

The beginning seedpoint was always the horizontal, mid-portion of the AF (hAF), defined in more detail later. Tractography was conducted sequentially and separately between a pair of seedpoints — e.g., always the hAF, and then one of four, separate cortical ROIs. The cortical ROIs included the anterior pars triangularis (A-PTr, defined later), posterior pars triangularis (P-PTr), POp, and vPMC.

Seedpoint placements for Broca's area and subregions within Broca's area

Placement for each cortical ROI was initially estimated using cortical reconstruction and volumetric segmentation from the FreeSurfer image analysis suite (Desikan et al., 2006). The automated cortical parcellation feature in FreeSurfer was used as an initial tool for the identification of POp and PTr on sagittal and axial slices. The ROIs for POp and PTr were then manually identified on a series of structural MRI sagittal and axial slices using TrackVis (Wang et al., 2007). Each target cortical ROI was drawn to the depth of the deepest sulcus for that ROI, in order to include the targeted white matter; these ROIs did not extend into the insula.

Five sulcal landmarks were visually identified on each subject's structural MRI scan in order to further define boundaries and placements for the PTr and POp target seedpoints (Amunts et al., 2004; Keller et al., 2007). See Fig. 2. These included the following: 1) the inferior frontal sulcus defined the superior border for POp and PTr; 2) the Sylvian fissure, the inferior border for POp and PTr; 3) the inferior precentral sulcus, the posterior border for POp; 4) the vertical, anterior ascending ramus (AR), the anterior border of POp and posterior border of PTr; and 5) the horizontal ramus (HR), the anterior border of PTr. Additionally, the PTr was further divided into anterior (A-PTr) and posterior (P-PTr) using the triangular sulcus as the dividing marker (Keller et al., 2007) (Fig. 2).

Without cytoarchitectonics, the issue of which anatomical landmark (sulcus) to use as a dividing marker between PTr and POp is not straightforward, especially if a diagonal sulcus (DS) is present. When present, the DS is located caudal to the vertical ascending ramus (AR) within the inferior frontal gyrus. Amunts et al. (2004) observed in their cytoarchitectonic studies, that a DS was present, however, only in every second hemisphere examined. They wrote that the DS can either mark the border between Brodmann area (BA) 45 and 44, or it can be inside BA 44. Thus, without cytoarchitectonics, it was not possible in the present study to know whether the DS, if present, was a border between PTr and POp, or if it was within the POp. Across our 8 subjects, 6 subjects (75%) had a DS in the LH; 4 subjects (50%) in the RH; and only 2 of those subjects had a DS in both. Therefore, for consistency across all subjects and both hemispheres, the AR was arbitrarily chosen to define the border between the PTr and POp in the LH and in the RH (Fig. 2).

Seedpoint placement for ventral premotor cortex

The sulcal boundaries defining the vPMC were the following: 1) the Sylvian fissure was defined as the inferior border; 2) the inferior

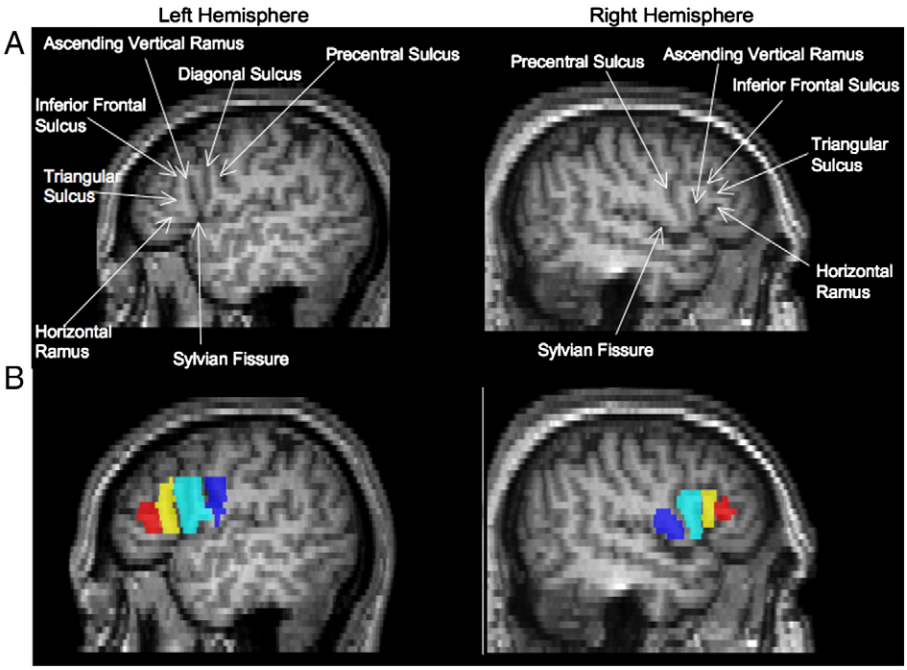

Fig. 2. (A) Sulcal landmarks used to define boundaries and location of the four cortical ROIs. The ascending vertical ramus was used to delimit PTr from POp in Broca's area. (B) Location of the four cortical ROIs in the LH and RH are superimposed on one of several sample sagittal slices used for ROI tracings. LH sample ROIs are for subject N4; RH sample ROIs are for subject N1. Colors: red, anterior PTr; yellow, posterior PTr; light blue, POp; and dark blue, ventral premotor cortex. Abbreviations: PTr, pars triangularis; POp, pars opercularis; ROI, region of interest; LH, left hemisphere; RH, right hemisphere.

frontal sulcus was extended caudally to define the superior border; 3) the inferior precentral sulcus, the anterior border; 4) the inferior central sulcus, the posterior border (Fig. 2).

Seedpoint placement for the horizontal, mid-portion of arcuate fasciculus (hAF)

The placement for this seedpoint was in the mid-portion of the horizontal aspect of the AF (hAF). A methodology similar to that of Makris et al. (2005), and Glasser and Rilling (2008) was used. The size of the entire hAF seedpoint was about 100 voxels in each hemisphere. It was drawn across 5–7 coronal slices on the DTI FA color map in TrackVis (Wang et al., 2007) (Fig. 3A). This region was superior to the insula, extreme capsule, claustrum, external capsule, and internal capsule (Fig. 3B). This region borders the SLF II and III (Makris et al., 2005; Glasser and Rilling, 2008). Thus, the hAF seedpoint could have included some of the SLF II and III fibers, because it is difficult to separate the AF from these SLF fibers.

Initial statistical analyses

Laterality index for each cortical ROI and the arcuate fasciculus

Because the study included a small number of subjects, a laterality index (LI) was first computed for relative L and R size of each ROI, in order to establish that the distribution of the relative L and R sizes for the seedpoints was not skewed in an atypical (rightward) direction. Either a leftward asymmetry or symmetry has been previously reported for the majority of subjects in studies that have examined relative size of total Broca's area, the PTr, the POp (Keller et al., 2009 for review); and the AF (Buchel et al., 2004; Nucifora et al., 2005; Parker et al., 2005; Hagmann et al., 2006; Powell et al., 2006; Vernooij et al., 2007; Upadhyay et al., 2008; Catani et al., 2007).

In the present study, the LI was computed using sample size (mm^3) for each L and R seedpoint, where $LI = L - R/(L + R) \times 100$. A positive LI value was considered to reflect leftward asymmetry; a negative LI value, rightward asymmetry. The LI for each seedpoint ROI (for each subject) is provided in Supplemental Table 1, and plotted in graph form in Supplemental Fig. 1.

Chi square results indicated that the probability of the relative size of the ROIs and volume of AF fibers being lateralized leftward or rightward, was not random ($x^2 = 15.55$, $df = 8$, $p = 0.05$), with a higher probability of being lateralized to the left. Since the relative sizes of the cortical ROIs, and volume of AF fibers in the LH and RH were not skewed in an atypical (rightward), direction this small population sample was considered to be not atypical of that found in previous studies, and further comparisons were performed.

Size of ROI cortical seedpoints

Additionally, to ensure that any potential white matter tractography volume differences would not be a direct result of differences in size of the ROI cortical seedpoints, statistical comparisons were performed for relative size of each cortical ROI. There were no significant differences in size of the ROI cortical seedpoints, with the exception of the following two: 1) the POp seedpoint was significantly larger ($p<0.05$) than the ipsilateral A-PTr and P-PTr in each hemisphere (Supplemental Table 1 and Supplemental Fig. 2C); 2) the POp seedpoint was also significantly larger ($p<0.05$) than the ipsilateral vPMC in each hemisphere (see Supplemental Table 1 for the means and SDs).

Volume of hAF

In order to establish the volume (mm^3) for the AF in each hemisphere, the TrackVis program was run for the hAF seedpoint *alone*, without any separate target, cortical ROI seedpoint. A paired *t*-test (2-tailed) was used to compare the volume of the AF fibers in the LH versus the RH. There was a significantly greater volume of AF fibers in the LH (mean = 6747.0 mm^3, SD = 2588.83) versus the RH (mean = 5842.7 mm^3, SD = 2353.99); ($t = 2.5$, $df = 7$, $p = 0.04$).

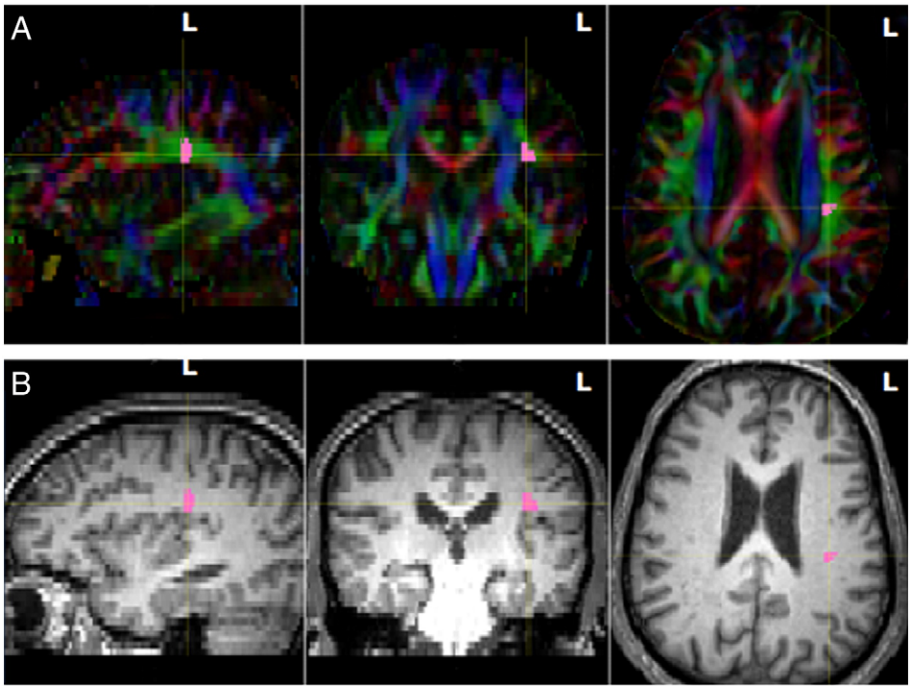

Fig. 3. Illustration of method used for locating the hAF seedpoint (pink) in sagittal, coronal and axial views in the LH (subject N4). The hAF seedpoint was drawn on 5–7 coronal slices in the horizontal mid-portion of the AF fibers oriented in the anterior–posterior direction (green). The AF seedpoint was located superior to the insula, extreme capsule, claustrum, external capsule, and internal capsule. A similar hAF seedpoint was drawn in the RH (not shown). (A) Fractional Anisotropy Color Maps; (B) Structural MRI Images. Abbreviations: hAF, horizontal mid-portion of the arcuate fasciculus; LH, left hemisphere; RH, right hemisphere.

Results

hAF pathways with separate cortical ROIs

hAF fiber tracts with anterior-PTr and posterior-PTr

Only one subject (N3) showed fiber tracts between the hAF and the entire PTr as a seedpoint (A-PTr plus the P-PTr combined) in either hemisphere. With PTr separated into anterior and posterior, no fiber tracts were observed between A-PTr and the hAF in the RH or LH, for all eight subjects (Table 1). Only one of the eight subjects showed fiber tracts between P-PTr and hAF in the RH and LH (subject N3).

hAF fiber tracts with pars opercularis

In contrast to PTr, 5/8 subjects showed pathways between R POp and R hAF, and all eight subjects showed pathways between L POp and L hAF (Table 1 and Fig. 4).

Because 3/8 subjects showed no fibers between R POp and R hAF (Table 1, N6, N7, N8), a paired *t*-test (2-tailed) was completed with only the five subjects who showed POp pathways with hAF in each hemisphere. There was no significant difference between the volume of hAF fibers to L POp (mean = 1961 mm^3, SD = 866) versus R POp (mean = 1177 mm^3, SD = 514); ($t = 1.75$, $df = 4$, $p = 0.15$) when only data for these five cases were compared.

hAF fiber tracts with ventral premotor cortex

Seven of eight subjects showed fiber tracts between R vPMC and R hAF; and all eight subjects, between L vPMC and L hAF (Table 1 and Fig. 4). Two of the three subjects who did not have pathways between R hAF and R POp, did have fiber tracts between R hAF and R vPMC (subjects N6, N8) (Table 1 and Fig. 4).

A paired *t*-test (2-tailed) was used to compare the volume of fibers between vPMC and hAF in the LH and RH, for all eight subjects. There was no significant difference in volume of L hAF fibers to L vPMC, (mean = 2266.5 mm^3, SD = 1668.16), versus R hAF fibers to R vPMC (mean = 1143.6 mm^3, SD = 685.85); ($t = 1.73$, $df = 7$, $p = 0.13$).

The observed presence of hAF fiber tracts with specific cortical ROIs was not dependent on sample size of the cortical ROIs. For example, in the RH, the seedpoint size for the vPMC was significantly smaller ($p < .05$) than that for the POp (see Supplemental Table 1 for means and SDs). However, in the RH, 7/8 subjects showed pathways between vPMC and hAF, but only 5/8 subjects showed pathways between POp and hAF. Similarly, in the LH, the seedpoint size for the vPMC was significantly smaller ($p < .05$) than that for the POp (see Supplemental Table 1). In the LH, all 8 subjects showed pathways between vPMC and hAF, as well as between POp and hAF.

Table 1
Volume of hAF fibers to each cortical ROI: subregions within Broca's area, and the ventral premotor cortex in the left hemisphere and the right hemisphere, for each subject. Abbreviations: hAF, horizontal mid-portion of arcuate fasciculus; A-PTr, anterior pars triangularis; P-PTr, posterior pars triangularis; POp, pars opercularis; vPMC, ventral premotor cortex.

	Left hAF fibers (mm^3) to each ROI				Right hAF fibers (mm^3) to each ROI			
	A-PTr	P-PTr	POp	vPMC	A-PTr	P-PTr	POp	vPMC
N1, 68 years, M	0	0	2707.0	63.2	0	0	1742.3	1679.1
N2, 57 years, M	0	0	1489.6	3635.3	0	0	1239.3	1275.8
N3, 58 years, M	0	668.3	1540.6	1222.3	0	733.9	1598.9	2245.3
N4, 55 years, M	0	0	3042.4	2240.5	0	0	600.2	527.3
N5, 58 years, F	0	0	1023.8	1134.0	0	0	706.3	907.2
N6, 69 years, F	0	0	2643.8	5287.7	0	0	0.0	1309.0
N7, 71 years, F	0	0	693.4	1483.9	0	0	0.0	0.0
N8, 62 years, M	0	0	1859.8	3065.0	0	0	0.0	1205.3
Mean	0	83.5	1875.0	2266.5	0	91.7	735.9	1143.6
SD	0	236.3	847.5	1668.2	0	259.5	722.6	685.8

Discussion

Our DTI study observed fiber tracts between hAF and POp and/or vPMC in both the RH and in the LH, but almost no fiber tracts between the hAF and the PTr in either hemisphere. In the RH, these findings are new. In the LH they support and replicate previous studies. For example, in the DTI studies of Frey et al. (2008) and Saur et al. (2008) pathways were observed between the L posterior Broca's area (not L anterior Broca's area) and the SMG via the AF (and likely SLF III). Frey et al., 2008 observed pathways between the L anterior Broca's area with the superior temporal gyrus to be via the extreme capsule, not via the AF. Thus, major pathways from premotor cortices in the LH have been observed to follow a more dorsal route via the AF/SLF III to SMG (Croxson et al., 2005; Frey et al., 2008; Saur et al., 2008); whereas major pathways from ventrolateral prefrontal cortex (including PTr) follow a more ventral route via extreme capsule, to part of the superior temporal gyrus, or middle temporal gyrus (Frey et al., 2008; Saur et al., 2008).

The dorsal route in the LH, as recently summarized by Frey et al. (2008), is mainly restricted to sensory-motor mapping of sound to articulation and higher-order articulatory control of speech, where the POp is connected directly with premotor area 6 (involved with orofacial musculature) (Petrides, 2006; Petrides et al., 2005). The ventral route in the LH likely performs linguistic processing of sound to meaning, requiring temporo-frontal interaction and top-down regulation of linguistic processing such as that involved in verbal retrieval (Petrides, 2006), and lexical/semantic aspects of language processing (Devlin et al., 2003; Gold and Buckner, 2002; Nixon et al., 2004; Poldrack et al., 1999; Price et al., 1996; Saur et al., 2008). A dissociation between the roles of L PTr versus L POp in semantic versus phonological tasks has been supported by TMS application to these two areas in normals, with differential/opposite effects observed (Gough et al., 2005).

The two parts of Broca's area differ in cytoarchitectonics. The PTr and the POp in both LH and RH, are often considered to correspond in a general manner with the cytoarchitectonic BA 45 and 44, respectively (Amunts et al., 1999, 2004). The primary distinguishing cytoarchitectonic feature between these two areas is located in cortical layer IV, which is granular in BA 45 and dysgranular in BA 44. The ventral premotor cortex (vPMC), located immediately posterior to BA 44, is agranular in layer IV (Amunts et al., 1999, 2004; Amunts and Zilles, 2006; Keller et al., 2009 for review). These differences in cytoarchitectonics may also support differences in connectivity and function for these two areas. In a detailed anatomical and fMRI study with verbal fluency, Amunts et al. (2004) described L BA 45 to be "involved in semantic aspects of language processing, while area 44 is probably involved in high-level aspects of programming speech production per se."

Our DTI results in the RH showed the presence of pathways between the hAF and the POp and/or vPMC, but not between the hAF and the PTr. Thus, there may be a dorsal route in the RH which is parallel to that in the LH. This dorsal route would include R hAF fiber tracts with R POp and vPMC which are likely connecting with R SMG (although this posterior pathway with SMG was not examined as part of our DTI study). Along these lines, a possible parallel role of the R POp might be related to articulation, and the R vPMC, to the movement of orofacial musculature (Petrides et al., 2005; Petrides, 2006). The relevance of a RH dorsal route in normal speech/language remains to be clarified; it may have relevance for speech/language recovery in aphasia, as discussed below.

A possible role for the R POp and R vPMC in promoting recovery of speech in nonfluent aphasia has been suggested since 1877, when Barlow reported his detailed anatomical study. The absence of any speech recovery following the second stroke, which destroyed the R POp and R vPMC (after initial destruction in the L POp and L vPMC when recovery did occur) suggests that following the first stroke, a

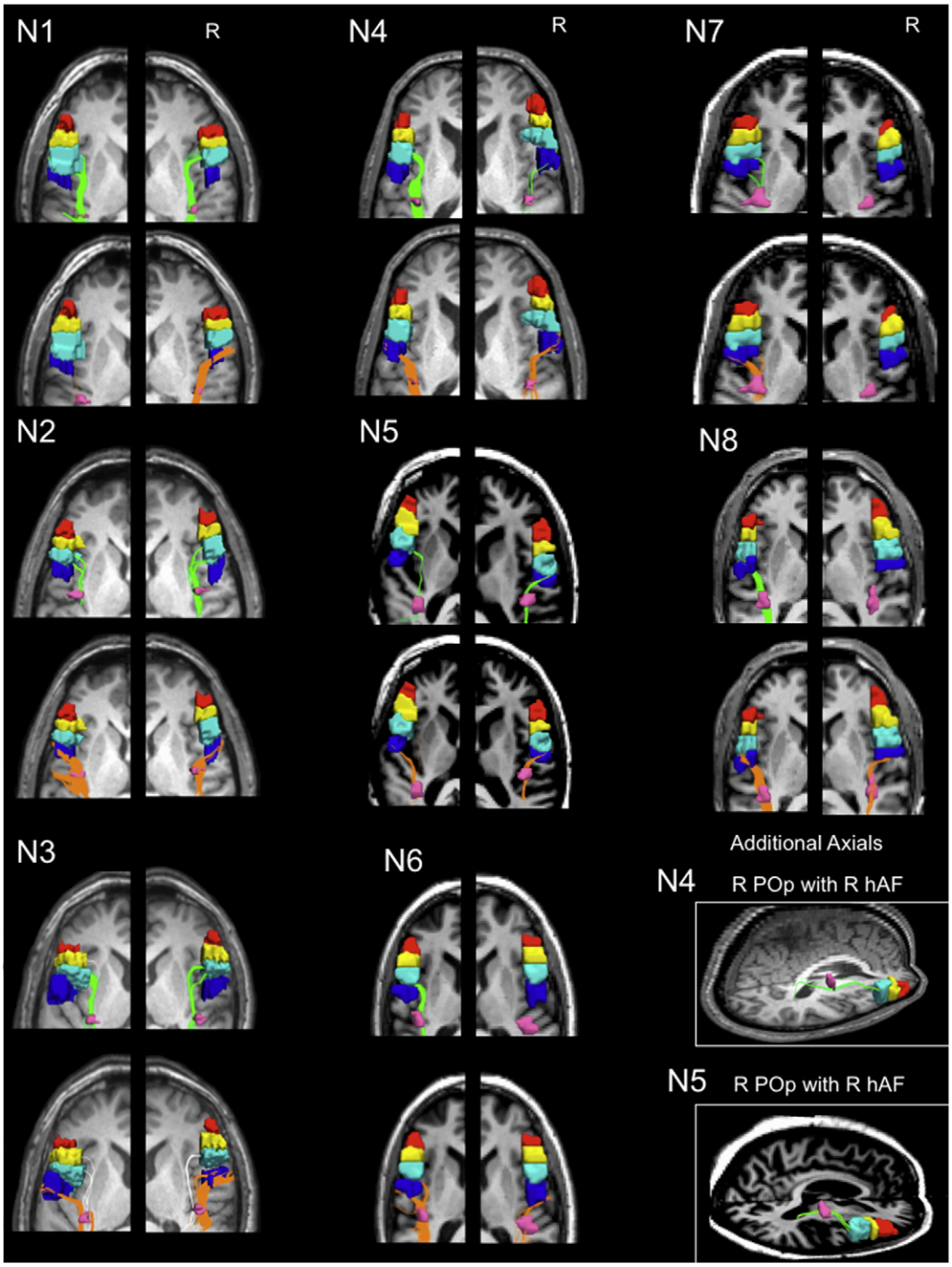

Fig. 4. Fiber tracts between the horizontal mid-portion of the AF (hAF) seedpoint (pink) and the separate cortical ROI seedpoints in the LH and RH for each subject. The cortical seedpoints are anterior PTr (red); posterior PTr (yellow); POp (light blue); and vPMC (dark blue). The fiber tracts between hAF and POp are shown in green; and those between hAF and POp, orange. Fiber tracts between hAF and posterior PTr (present only in N3) are shown in white (shown on the same slice as those for vPMC, to conserve space; tractography was performed separately between hAF and each cortical ROI seedpoint). There were no fiber tracts between hAF and A-PTr in either hemisphere for any subjects. See Table 1. Additional axial views are provided for subjects N4 and N5, showing fiber tracts between the hAF and R POp, where view of R POp was obscured by the presence of R vPMC on other axial views above, for these two subjects. Abbreviations: hAF, horizontal, mid-portion arcuate fasciculus; POp, pars opercularis; PTr, pars triangularis; vPMC, ventral premotor cortex.

supportive, parallel system for orofacial musculature and articulation had possibly been present in the R POp and R vPMC (Fig. 1).

In addition, the PET study by Blank et al. (2003), observed that after lesion of the L POp, the R POp "contributed to processes involved in the assembly of the sound structure of speech." Results from our rTMS studies in nonfluent aphasia patients also suggest a possible role for the R POp in recovery of speech following L frontal lesion, where suppression of R POp with 1 Hz rTMS was observed to *impair* naming in some aphasia cases (Naeser et al., 2002, 2005b). Suppression of R POp with 1 Hz rTMS would likely interrupt connections between R POp and R vPMC, as well as connections via the "dorsal route" to R SMG and directly interrupting control of articulation and orofacial musculature, as well as indirectly interrupting connections with other parts of the bilateral neural network for naming (Price et al., 2001; Gold and Buckner, 2002; Damasio et al., 2004).

Conversely, we have observed that suppression of the R PTr with rTMS *improves* naming in nonfluent aphasia. Although the mechanism for this beneficial effect is unknown, we would posit the following possibility: in cases with nonfluent aphasia where lesion is present in L inferior frontal cortex, and/or subcortical white matter deep to it (adjacent to ventricle), possible hyperactivity of neurons in R PTr (among other RH areas) may be present, due to interhemispheric disinhibition from the damaged L frontal lobe. This R PTr hyperactivity could excessively suppress the R POp, via their shared U-fibers, which could possibly hinder recovery from aphasia.

The POp (BA 44) and PMC (BA 6) in the human brain are thought to be analogous to the monkey's F5 region, a locus of mirror neurons (Rizzolatti and Craighero, 2004). The mirror neuron system is bilateral, and these neurons fire during both production and perception of similar actions (Wilson et al., 2004; Iacoboni, 2008 for review). They are important in child language acquisition (Rizzolatti and Craighero, 2004). The potential contribution of parts of the mirror neuron system to recovery in aphasia is unknown; however, some of the results post-rTMS in our aphasia patients may provide some insight. For example, one category of naming where we have consistently observed improvement is that of naming "tools/implements" (Naeser et al., 2005a,b, 2010; Martin et al., 2009; Hamilton et al., 2010). Although hypothetical at this time, this may be related in part, to the mirror neuron system. The POp (BA 44, an area with mirror neurons) "mediates observation–execution matching for the goals of arm/hand actions" (Kemmerer and Gonzalez-Castillo, 2010, for review); and the neural network for "tool use" is widely distributed, including temporal, parietal and frontal regions in the LH (Kemmerer et al., 2008). Thus, following rTMS suppression of R PTr, modulation of R POp (and vPMC) may have permitted access to this uniquely, widespread neural network for naming tools/implements. These possibilities require further study.

The results from the present DTI study suggest that in the RH the fiber tracts between the hAF and POp and vPMC may be parallel, and similar in structure to those in the LH. The relevance of these similarities for speech/language in normals, and for aphasia recovery in stroke patients remains to be further explored.

Limitations

Some limitations may have restricted our findings.

1) Even though DTI has been prevalently used to analyze white matter connectivity, it has inherent limitations. The deterministic tractography algorithm used here is unable to track through areas of crossing fibers when a competing pathway is significantly stronger, or when subject motion reduces the quality of the dataset. Multi-fiber orientations within a voxel are not captured robustly by deterministic tracking, thus limiting tracking performance to areas of high anisotropy and low uncertainty. Weak pathways would be more reliably found with the probabilistic algorithm (Behrens et al., 2007). However, even with this limitation in methodology, we were able to replicate previously published findings for the LH, where the hAF was observed to have fiber tracts with POp and vPMC, but not with PTr, in most subjects.
2) The AF is located parallel to the inferior part of the SLF II and SLF III. The SLF III has been found to connect BA 40 (SMG) with BA 44 (POp) and ventral BA 6 (vPMC) (Croxson et al., 2005; Makris et al., 2005; Rushworth et al., 2006). We observed hAF pathways with POp and vPMC in each hemisphere; our designated hAF could have included some of the SLF III.
3) The present study only examined fiber tracts between the horizontal mid-portion of the AF to parts of Broca's area, and the vPMC, not pathways caudal to the mid-portion of the AF towards parieto-temporal areas. Nor did we examine the extreme capsule connections. Although our results support the notion of a dorsal route with fiber tracts between the hAF, and the POp and vPMC (but not PTr) in each hemisphere, we cannot comment directly on a possible ventral route for the PTr with the extreme capsule. A more detailed mapping of complete white matter pathway connections between parts of R Broca's homologue and the vPMC in the RH, with specific posterior zones (inferior parietal and/or superior and middle temporal gyrus areas) was beyond the scope of this study, and would be appropriate for a future study.
4) The relatively older ages of the healthy subjects in this study may have affected the data, and reduced the potential pathways observed from the hAF to the cortical target ROIs. If younger subjects had been studied, it is possible that additional white matter tracts could have been observed. These ages were chosen, however, so that future comparisons could be performed with aphasic stroke patients of a comparable age.
5) The number of subjects examined in this DTI study was small, with only eight healthy controls. However, the major observations were consistent across the majority of subjects — e.g., there was a dorsal route pathway between the hAF with the POp and vPMC (but not with the PTr), in both the RH and the LH. Also, our initial LI analyses showed that relative sizes for the L and R ROIs, and the relative volume of the AF fibers, were not skewed in the atypical (rightward) direction for this small population sample.

Conclusions

We observed the hAF fiber tracts were primarily with the POp and the vPMC (not with the PTr) in each hemisphere; these pathways likely followed the dorsal route pathway to SMG, as has been previously described in the LH, but not studied here. These results suggest different network connections, and different language roles for the two parts of Broca's area, POp and PTr. In aphasia recovery, the POp and the vPMC may support a common role (primarily orofacial musculature and articulation) which is different from that of the PTr. Further examination of these pathways in both aphasia patients and controls with a probabilistic algorithm, and their connections with the bilateral neural networks for speech/language and naming is recommended.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2010.04.247.

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