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Bidirectional iterative parcellation of diffusion weighted imaging data: Separating cortical regions connected by the arcuate fasciculus and extreme capsule

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Abstract

This paper introduces a Bidirectional Iterative Parcellation (*BIP*) procedure designed to identify the location and size of connected cortical regions (*parcellations*) at **both** ends of a white matter tract in diffusion weighted images. The procedure applies the FSL option “probabilistic tracking with classification targets” in a bidirectional and iterative manner. To assess the utility of BIP, we applied the procedure to the problem of parcellating a limited set of well-established gray matter seed regions associated with the dorsal (arcuate fasciculus/superior longitudinal fasciculus) and ventral (extreme capsule fiber system) white matter tracts in the language networks of 97 participants. These left hemisphere seed regions and the two white matter tracts, along with their right hemisphere homologues, provided an excellent test case for BIP because the resulting parcellations overlap and their connectivity via the arcuate fasciculi and extreme capsule fiber systems are well studied. The procedure yielded both confirmatory and novel findings. Specifically, BIP confirmed that each tract connects within the seed regions in unique, but expected ways. Novel findings included increasingly left-lateralized parcellations associated with the arcuate fasciculus/superior longitudinal fasciculus as a function of age and education. These results demonstrate that BIP is an easily implemented technique that successfully confirmed cortical connectivity patterns predicted in the literature, and has the potential to provide new insights regarding the architecture of the brain.

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Keywords

arcuate fasciculus; diffusion-weighted imaging; extreme capsule; laterality; parcellation; superior longitudinal fasciculus

1. Introduction

Brain networks are composed of gray matter regions that demonstrate functional specialization and the white matter tracts that provide structural connectivity among these regions. One non-invasive technique for identifying the relationship between gray matter regions and the associated white matter tracts is parcellation of diffusion weighted imaging (DWI) data (Anwander et al., 2007; Behrens et al., 2003). DWI parcellation techniques define cortical regions by their connectional architecture (Behrens and Johansen-Berg, 2005; Johansen-Berg et al., 2005). In other words, anatomically – and likely functionally – distinct regions of the cortex are identified based on their white matter connections (Johansen-Berg, 2004). The technique was first implemented by Behrens and colleagues (2003) who categorized gray matter voxels in the thalamus (seed) based on connectivity to gray matter in the major lobes of the brain (targets). Using a different algorithm, Anwander and colleagues (2007) categorized voxels at the gray-white boundary of the inferior frontal gyrus (seed) based on connectivity to the entire white matter volume (target). In both cases, the parcellation procedure served to categorize the voxels in a single seed area based on connectivity.

To our knowledge, a parcellation procedure has not been fully elaborated to identify the cortical connectivity at **both** ends of a white matter tract. Such a procedure would be of considerable value because it would characterize a candidate cortical circuit more completely than standard tractography. Behrens and colleagues (2003) recognized the issue and suggested that voxels with a high probability of connecting to a particular target could be used in a tracking seed to determine where they were most likely to connect within the target. We took their suggestion a step further and developed a procedure we call *bidirectional iterative parcellation* (BIP) intended to identify the location and size of connected regions at both ends of an established tract. BIP isolates two cortical regions connected by a white matter tract by “shrinking” liberally defined initial seed regions. To implement BIP, we used the probabilistic tractography algorithm developed by Behrens and colleagues (2003) and available as part of the FSL software package (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/>). This algorithm permitted us to choose standard space gray matter regions as seeds and targets, making the approach more automatic than selecting gray-white boundary voxels as required by the Anwander et al. (2007) approach. The final outcome identified connected gray matter regions as well as providing a conservative map of the selected tract.

The purpose of the current paper was to examine the BIP analysis for an anterior seed located in inferior frontal cortex and a posterior seed in posterior temporal and inferior parietal cortex. Regions within these seeds are connected by the arcuate fasciculus/superior longitudinal fasciculus (AF) complex and/or the extreme capsule (EmC) fiber system (a.k.a. inferior frontal occipital fasciculus). Although these regions are only a subset of the areas

likely to be connected by either tract (see Martino et al., 2010; Sarubbo et al., 2013), they provide an excellent test case for BIP because the AF and EmC connect adjacent and/or overlapping regions of cortex within the seed regions. These cortical regions and tracts are of particular interest in models of speech and language because they are part of anatomically separate dorsal and ventral information processing streams (Axe et al., 2013; Saur et al., 2010) whose specific functional roles are a current topic of debate (see e.g., Friederici, 2009; Griffiths et al., 2013; Rolheiser et al., 2011).

Previous studies that tracked both the AF and EmC have distinguished the two tracts by starting with different seed regions for either the anterior or posterior termini. In some studies, distinct seed regions for the two tracts were selected using prior anatomical knowledge about the trajectory or termination of the tracts (Brauer et al., 2013; Croxson et al., 2005; Frey et al., 2008; Rolheiser et al., 2011). In other studies, seed regions were defined by the location of task-related activity in fMRI experiments (Brauer et al., 2011; Griffiths et al., 2013; Saur et al., 2008, 2010). These methods have met with demonstrable success. For instance, by defining two different anterior seed regions in the left inferior frontal gyrus (pars opercularis and pars triangularis), Griffiths et al. (2013) demonstrated a connection between pars opercularis and a region-of-interest in the temporal lobe via the AF, and a separate connection between that same temporal region-of-interest and pars triangularis via the EmC. However, prescribing distinct seed regions in advance does not allow discovery of cortical parcellations at both ends of a tract; BIP was designed to address this problem.

Because the BIP procedure is new, we aimed to test it relative to the existing literature regarding the frontal and temporoparietal termini of the AF and EmC. To be clear, the goal of the paper was not to identify all terminal endpoints for the two tracks, but rather to test the BIP procedure for predictions within specified regions of interest. We review the relevant literature and expectations below.

1.1 Anterior origins of the two tracts

Based on dissection, DWI, and fMRI resting-state connectivity studies, there is a general consensus that within the inferior frontal gyrus, the origin/terminus of the AF is more posterior than that of the EmC (Croxson et al., 2005; Frey et al., 2008; Petrides and Pandya, 2009; Sarubbo et al., 2013; Saur et al., 2008, 2010; Xiang et al., 2010; see Dick and Tremblay, 2012 for review). We thus predicted that within our inferior frontal gyrus seed region, the AF would connect primarily to pars opercularis and pars triangularis, whereas the EmC would connect primarily to pars triangularis and pars orbitalis (see Sarubbo et al., 2013). Additionally, based on dissection, Sarubbo et al. (2013) reported that AF fibers were more lateral (superficial) than EmC fibers. Therefore, we expected that within our anterior seed regions, AF termini would be lateral to EmC termini. We acknowledge that other anterior termini are likely connected to the AF and EmC. For example, both the AF and EmC may have termini in middle frontal gyrus (Martino et al., 2013; Sarubbo et al., 2013). One branch of the AF may connect to premotor areas (Martino et al., 2013), and one branch of the EmC likely connects to frontal pole (Sarubbo et al., 2013). Critically, the fact that both of these anatomically dissociable pathways have well-studied termini in the inferior

frontal gyrus provides a stringent test of the BIP procedure. In particular, the wealth of literature on connectivity of the AF and EmC to the left inferior frontal gyrus led us to define an anterior seed that included regions reported to connect primarily to AF, regions reported to connect primarily to EmC, and regions reported to connect to both tracts. This composition of the seed region was crucial to evaluating whether the BIP procedure could differentiate gray matter connected to one tract versus the other.

1.2 Posterior origins of the two tracts

Many authors report that the posterior origin/terminus of the EmC lies primarily in the superior and middle temporal gyri (see Martino et al., 2013). Although several authors report a terminus of the EmC in angular gyrus (Agosta et al., 2010; Frey et al., 2008; Makris and Pandya, 2009; Weiller et al., 2011), not all authors agree (see Martino et al., 2010). In fact, what we have termed the EmC corresponds to what other authors call the inferior frontal occipital fasciculus. The inferior frontal occipital fasciculus is a complex bundle that can be divided into superficial and deep layers (Martino et al., 2010). Based on the termini we choose for this analysis, the EmC corresponds most closely to the superficial layer of the inferior frontal occipital fasciculus. Even so, we examine only a subset of the termini associated with this superficial bundle (Martino et al., 2010; Sarubbo et al., 2013).

The exact origin of the arcuate/superior longitudinal fasciculus projection to the inferior frontal gyrus is also unclear due to the difficulty of separating the various parts of the tract complex (Dick and Tremblay, 2012). Many investigators reserve the term “arcuate” for a tract arising in the superior (Frey et al., 2008) and middle temporal gyri (Agosta et al., 2010). However, other investigators report additional termini for the arcuate in inferior temporal gyrus (Martino et al. 2013) and the occipital lobe (Martino et al., 2010). Fibers that connect the supramarginal/angular gyri with prefrontal regions are then labeled as a different branch of the superior longitudinal fasciculus (i.e., “SLFIII” or the “anterior segment of the SLF”). There has been some dispute as to whether fibers from the supramarginal/angular gyri actually reach the inferior frontal gyrus or terminate only in a premotor region located more dorsally (see e.g., Frey et al., 2008 and Martino et al., 2013 for different conclusions, and Dick and Tremblay, 2013 for review). Given this ambiguity and the possibility that this DWI data does not reliably separate these fiber bundles, we adopt the label “AF” to refer to this dorsal connection between temporoparietal regions and the inferior frontal gyrus. Regardless of the difficulty in distinguishing portions of the arcuate fasciculus/superior longitudinal fasciculus complex, extant data suggest that the posterior cortical parcellation of this tract (or tracts) should be located somewhat posterior and superior to that of the EmC and thus it should include a larger parietal component. Based on dissection, AF fibers were also found to be more lateral than EmC fibers (i.e., superficial inferior frontal occipital fasciculus) at their posterior termini (Martino et al., 2010). We thus expected to find that AF termini might be lateral to EmC termini in our posterior seeds.

1.3 Hemispheric asymmetry of the AF

Numerous studies have examined the hemispheric asymmetry of the AF, with the expectation that it would be left-lateralized due to its association with speech and language. Larger volumes, more tract streamlines and/or higher fractional anisotropy in the left than

right hemisphere have been found in studies with broad definitions of the AF or those that used a target region-of-interest in the superior temporal gyrus (Glasser and Rilling, 2008; Lebel and Beaulieu, 2009; Parker et al., 2005; Powell et al., 2006; Vernooij et al., 2007). Other studies that have divided the AF into fronto-temporal and fronto-parietal segments report that the fronto-temporal segment is left-lateralized whereas the fronto-parietal segment is right-lateralized (Catani et al., 2007; Euvathingal et al., 2007; Thiebaut de Schotten et al., 2011) or bilaterally symmetric (Matsumoto et al., 2008). Here, we do not attempt to subdivide the AF into fronto-temporal versus frontal-parietal segments, but instead use a temporoparietal seed/target region, so that we have no predictions about asymmetry of the tract volume *per se*. However, the latter set of studies suggests a prediction about the AF-connected temporoparietal parcellation, namely that the portion falling within the temporal lobe may be larger in the left hemisphere whereas the portion falling within the parietal lobe may be larger in the right hemisphere.

1.4 Hemispheric asymmetry of the extreme capsule

In contrast to the AF, hemispheric asymmetries in the EmC connection between inferior frontal and temporoparietal areas have received little attention. Makris and Pandya (2009) reported larger volumes but lower fractional anisotropy in the right hemisphere in a small sample of five participants that did not allow statistical analysis. Additional exploration of the hemispheric asymmetry of the extreme capsule and selected cortical parcellations is warranted.

1.5 Hemispheric asymmetry and language lateralization

Reports of strong left-hemisphere language lateralization and related hemispheric asymmetry (Falzi et al., 1982; Toga and Thompson, 2003; Vernooij et al., 2007) must be tempered by recent evidence about the complexity of lateralization (see Pinel and Dehaene, 2010). First, the incidence of atypical language lateralization may be relatively high: 8% among right-handers, 15% in ambidextrous individuals and 27% in strong left-handers (Knecht et al., 2000), and when atypical lateralization does occur, it does not necessarily correspond to atypical language skills (Bishop, 2013). Second, recent evidence suggests an uncertain relationship between language-lateralization and hemispheric asymmetries (Vernooij et al., 2007; Keller et al., 2011). For example, Keller and colleagues (2011) reported that Broca's area was so difficult to define that they could not establish any relationship between asymmetries in this region and language dominance, but the planum temporale was left-lateralized regardless of language dominance. In addition, Thiebaut de Schotten and colleagues (2011) reported that language lateralization was not correlated to AF tract volume. These recent studies suggest that temporal gray matter termini may be left-lateralized but that inferior frontal gray matter termini may not be. Because we do not differentiate the fronto-temporal and fronto-parietal segments of the AF, we might also not expect to identify lateralization of the AF tract.

1.6 Hemispheric asymmetry and demographic factors

Gender, handedness, age, and education may also affect hemispheric asymmetries. Recent research reports no association between gender and language lateralization (Berl et al., 2014;

Knecht et al., 2000; Pinel and Dehaene, 2010; Plante et al., 2006; Sommer et al., 2008), although some researchers report a relationship between gender and hemispheric asymmetries (see Toga and Thompson, 2003 for review). Similarly, although left-handed and ambidextrous individuals may be more likely to show departures from left hemisphere language lateralization (Knecht et al., 2000; Szaflarski et al., 2012), handedness is not a strong predictor of hemispheric asymmetries (Toga and Thompson, 2003). In contrast, recent studies spanning the age range from infancy to young adulthood indicate that both language processing and related hemispheric asymmetries become increasingly left-lateralized with maturation (Berl et al., 2014; Brauer et al., 2013; Holland et al., 2007; Minagawa-Kawai et al., 2011; Plante et al., 2006; Toga and Thompson, 2003). This maturation occurs at different rates in different parts of the language network. Specifically, the EmC is thought to develop before the AF (Brauer et al., 2013; Perani et al., 2011) and temporal areas are thought to develop before inferior frontal areas (Berl et al., 2014). Although few studies have examined structural changes to language areas in adulthood, certain components of language (e.g., low frequency vocabulary) continue to develop in adulthood and as education becomes more advanced (Ramscar et al., 2014). Mårtensson and colleagues (2012) reported that both anterior and posterior language areas undergo volumetric expansion in interpreters learning a new language. In addition, AF tract volume is reported to be larger in musicians, especially singers, than in non-musicians (Halwani et al., 2011) and musical education has been shown to enhance language skills (Milavonov et al., 2011). Given evidence regarding the sensitivity of language regions to experience, the present study examines volumetric differences correlated to maturation and education with the expectation that the language system may continue to evolve throughout the lifespan.

2. Methods

2.1 Participants

Brain scans from 97 adults (62 women and 35 men) were evaluated for this study. They ranged in age from 18 to 84 years (mean = 47.7 years, SD = 21.5); men and women did not differ in age ($t(95) = -0.25, p > .05$). Eighty-one participants were right-handed; sixteen were left-handed or ambidextrous. Years of formal education ranged from 12 to 20 (mean 15.5 years, SD 2.6; with 12 years assigned to high school graduation, 16 for a bachelors degree and 20 for a doctorate). All participants were free from psychoactive medications, had no history of head injury, neurological or psychiatric disorders by self-report, and reported no heavy drug or alcohol use. All participants 65 and older completed the Mini-Mental-State exam and scored at or above the normative mean for their age and educational level (Crum et al., 1993).

2.2 Scanning

Brain scans were acquired on a “long bore” General Electric 3.0T HD 12x Signa Excite scanner with a bore 55 cm in diameter. It was equipped with an 8 channel HR brain array and optimized ACGD gradients (40mT/m, 150 mT/m/ms slew rate).

An echo planar DWI sequence was acquired with parallel imaging (TR 13,000, TE 72.3, NEX 2, flip angle 90, FOV 333, matrix 128x128, 57 contiguous slices, voxel dimension

2.6x2.6x2.6mm isotropic, directions 25, B 1000). Parallel imaging reduces echo planar distortion ~50%, and decreases signal to noise ratio ~15%, making 3.0T scanning with parallel imaging an optimal combination for DWI (Alexander et al., 2006). We set the scanner to prevent upscanning, because this would have resliced voxels in-plane (but not between planes) producing nonisotropic voxels and distorting the vectors needed for tractography. The isotropic voxels resulting from this precaution benefit tractography because they reduce partial voluming and improve signal to noise ratio (Fujiwara et al., 2007). For each participant we also collected three B0 images (Jones et al., 1999).

Two structural images, a FLAIR and SPGR, were used for segmentation and registration. The FLAIR (TR 11002, TE 123.714, flip angle 90, FOV 256, matrix 256x256, 57 contiguous slices, voxel dimension 1x1x2.6 mm) was acquired in the same plane as the DWI and was used to identify white matter hyperintensities and linearly register the DWI to the SPGR. The SPGR was used to linearly register participants to standard space and was acquired in the sagittal plane with one of two protocols: (1) TR 5.145, TE 1.988, inversion time 500, NEX 1, flip angle 15, FOV 256, matrix 256x256, 136 contiguous slices, voxel dimension 1x1x1.4 mm or (2) TR 11 ms, TE 1.876 ms, inversion time 500, NEX 1, flip angle 15, FOV 333, matrix 256x256, 136 contiguous slices, voxel dimension 1.3x1.3x1.3 mm). In addition, we used the SPGR to estimate cranial vault as the total volume of brain tissue and cerebrospinal fluid (CSF).

2.3 Analysis

We ran all processing on Intel Mac Pro computers with OSX 10.7 and 64 bit FSL 4.1.9 (Gronenschild et al., 2012, Jenkinson et al., 2012). The DWI preprocessing pipeline consisted of eddy current correction, local diffusion parameter modeling and diffusion tensor fitting.

AF- and EmC-connected cortical regions were identified using “probabilistic tracking with classification targets” in FSL, applied iteratively and bidirectionally. Specifically, this process started with the designation of an initial seed area from which tracking of fiber pathways began, and an initial target area at which fiber pathways terminated. Five thousand streamlines were then generated from each voxel in the seed area. Only those streamlines that reached the target area were retained. Likewise, only those seed voxels that generated streamlines reaching the target area were retained (Behrens et al., 2003). For the bidirectional iterative procedure demonstrated here, we used the voxels retained in the seed after the first step as the target for the next iteration, and we used the target of the first step as the seed for the next iteration. Successive iterations shrank the connected regions until they disappeared or stabilized (i.e., two successive iterations had the same-sized parcellations). If a connected region disappeared, then the associated tract and the other connected region also disappeared. If the connected regions stabilized, they constituted the final parcellations for the tract.

To test the BIP procedure, we needed to guarantee that only the difference in tract – AF versus EmC – and not the difference in initial seed or target areas would dictate the outcome. Therefore, in each hemisphere, the two initial areas supplied as seeds and targets to BIP were exactly the same for both tracts: an inferior frontal area and a temporoparietal

area (Figure 1a, b, c). The inferior frontal area and its right homologue consisted of three anatomical subregions: (1) pars opercularis (BA 44); (2) pars triangularis (BA 45); and (3) pars orbitalis (BA 47). The AF and EmC likely project to other regions of frontal cortex, but these were not examined here. The temporoparietal seed/target region for both tracts included four anatomical subregions in each hemisphere: posterior middle temporal, posterior superior temporal, supramarginal and angular gyri. Again, the AF and EmC likely project to other temporoparietal or even occipital regions, but these were not examined here because our goal was to determine the performance of the BIP procedure in an extensively studied set of termini that might be targeted by both tracts. The established language regions we chose as seeds provide such a set of termini. All anatomical subregions were derived from the Harvard-Oxford cortical atlas in FSL (http://www.cma.mgh.harvard.edu/fsl_atlas.html; Desikan et al., 2006), and registered into subject space before being combined. For every participant, we ran BIP to define each tract and this limited set of cortical parcellations in both hemispheres.

To improve the accuracy of the BIP procedure we imposed two spatial priors (Jbabdi, 2011). First, we constrained BIP to either the dorsal or ventral route with liberal termination masks (Figure 2). These masks were designed to prevent tracking into the anterior temporal lobe, the opposite hemisphere or the territory of the other tract. To create these masks we added the initial seed regions to the dilated tractography results from three dozen subjects. We then inverted and manually edited these results to allow a wide path through either the dorsal or ventral route, but not both. Without such constraint, we found that tractography often connected the AF and EmC in a loop.

Second, we created a cerebrospinal fluid mask in DWI space to prevent tracking across regions of CSF. Because white matter hyperintensities are often erroneously segmented as CSF in DWI images, one author (DP) reviewed all FLAIR images for the presence of white matter hyperintensities, and a mask was created as necessary using an automated algorithm (Wu et al., 2006). For younger participants (ages 18–50), there were no problematic white matter hyperintensities; for older participants (age > 50), the hyperintensity mask was then subtracted from the CSF mask. The resulting CSF masks were reviewed to insure that: (a) they did not cover tissue with higher than average fractional anisotropy; (b) they included the sylvian fissure, which is an important boundary for differentiating the AF and EmC; and (c) white matter hyperintensities were not erroneously included in CSF masks.

In order to address the potential problem that probabilistic tractography can be overly enthusiastic, final tracts and parcellations were thresholded and masked with the appropriate tissue type. Specifically, final tracts from “seed to target” and “target to seed” were averaged, thresholded at 5% probability, binarized, warped into standard space and masked with a whole brain white matter segmentation. Final parcellations were warped into standard space and masked with a whole brain gray matter segmentation.

To insure that motion during DWI acquisition did not account for our measures (Yendiki et al., 2013) we correlated mean and maximum motion for each subject to age and volumetric measures. We used the root mean square deviations between consecutive volumes as a measure of motion. These deviations include the effects of both translation and rotation.

For our chosen seed regions, we performed analyses to characterize (1) the spatial separation of and (2) relative locations of contiguous parcellations, as well as (3) tract connectivity, (4) volume lateralization, and (5) volume variation based on demographic factors.

To determine spatial separation of contiguous AF and EmC parcellations in each of the four areas (left inferior frontal, left temporoparietal, right inferior frontal, and right temporoparietal), we used the Jaccard index. This standardized measure provides an index of similarity for which 0 indicates no spatial overlap between regions (complete segregation) and 1 indicates complete spatial overlap (Shattuck et al., 2009). The spatial separation analysis indicated the similarity of contiguous AF- and EmC-connected cortical regions, but not their relative locations.

To compare the relative locations of the contiguous cortical regions, we compared their centers-of-gravity. We operationalized the center-of-gravity as coordinates on each of the three orthogonal axes (x, y, z). Coordinate comparison using paired t-tests revealed the relative locations (lateral-medial, anterior-posterior, superior-inferior) of the connected cortical regions and whether those locations differed significantly. Coordinate comparison, however, does not indicate the connectivity of tracts to anatomical subregions.

To characterize tract connectivity, we determined the relative distribution of each parcellation across anatomical subregions in either the inferior frontal or temporoparietal areas [Tables 3, 5]. We used percent overlap as a measure of the relative distribution of the parcellation. For example, a small parcellation (10 voxels) and a large parcellation (100 voxels) could have equivalent distributions if the small parcellation was divided such that nine voxels fell into one subregion and one voxel fell into the other subregion, whereas the large parcellation was divided such that ninety voxels fell into one subregion and ten voxels fell into the other subregion. The relative distribution is the same although the absolute volumes differ. In addition, we examine individual variability. We display this variability in Figures 3 and 4 and we identify the percentage of participants who display connections to each anatomical subregion in Tables 3 and 5. These simple representations of individual variability provide insights that average connectivity does not convey.

Finally, we characterized volume lateralization of tracts and parcellations in the whole group and as a function of potentially relevant demographic variables (gender, handedness, age, education, and cranial vault). Here we are interested in comparing the absolute size of both the tract and parcellation volumes rather than comparing the relative distribution of a parcellation across anatomical subregions. Following Galaburda et al. (1987), we used delta to measure laterality as follows: $(\delta = (R - L) / ((R + L) * 0.5))$. Positive values indicate rightward asymmetry whereas negative values indicate leftward asymmetry. However, overall statistical patterns do not capture information about how many participants are strongly lateralized. That is, if a particular volume is strongly left-lateralized in half the participants and strongly right-lateralized in the other half, that will look equivalent to all the participants having a bilateral distribution. To capture this distinction, for each volume of interest we divided participants into groups based on their laterality index: right-lateralized ($\delta > .1$); left-lateralized ($\delta < -.1$) and bilateral (δ between $-.1$ and $.1$) [Table 7].

3. Results

Throughout the results section, we report standard space values for consistency and ease of comparison to the literature. However, we separately confirmed that laterality indices and tract and parcellation volumes are highly correlated between native and standard space ($r = .961 - .978$, all $p < .000001$).

Across the 97 participants, BIP yielded stable solutions for the AF in 95 left and 94 right hemispheres; and for the EmC in 89 left and 81 right hemispheres. On average, there were fewer iterations when stability was not attained (mean=3.51, SD=1.33, Range 2–8) than when stability was attained (mean=10.83, SD=2.48, Range=4–18). For the stable solutions, number of iterations was negatively correlated to age ($r = -.21$; $p < .0001$) and maximum motion ($r = -.12$; $p < .05$) but positively correlated to the size of the initial seed ($r > .17$, $p < .001$) and the final parcellation ($r > .41$, $p < .00001$). Neither tract ($t(357)=0.41$, $p > .05$) nor hemisphere ($t(357)=0.37$, $p > .05$) predicted number of iterations. The age of participants with successful parcellations did not differ from the age of participants with unsuccessful parcellations (AF, $t(192) = 1.11$, $p > .05$; EmC, $t(192) = 0.92$, $p > .05$). Although maximum motion was significantly correlated to age ($r = .44$, $p < .0001$), motion was not significantly correlated to the volumes of connected cortical parcellations ($r = .02$ to $.20$, all $p > .05$) regardless of whether we included data from unsuccessful parcellations. Motion also did not correlate to tract volume for successful parcellations ($r = .04$ to $.16$, all $p > .05$). However, if unsuccessful parcellation data were included, the left EmC tract volume was correlated to maximum motion ($r = -.22$, $p < .05$). Because our participants appeared to be neurologically normal and BIP was likely to under-identify connected regions rather than over-identify them, we excluded unsuccessful parcellations from subsequent analyses rather than attributing these failures to underlying anatomy.

Figure 1(d, e, f) shows group-averaged cortical parcellations and tracts in both hemispheres. Connected cortical parcellation volumes were positively correlated with each other ($r = .35$ to $.52$ across the four pairs of connected parcellations, all $p < .001$). In addition, each cortical parcellation volume was correlated to the volume of the connected tract ($r = .60$ to $.77$, all $p < .001$).

3.1 Spatial separation of parcellations

We used the Jaccard index to assess the spatial separation of contiguous AF and EmC parcellations in each of the four areas (left inferior frontal, left temporoparietal, right inferior frontal, and right temporoparietal) for every participant. Contiguous AF- and EmC-connected parcellations showed very good spatial separation (mean Jaccard indices of $.01$ to $.04$, SDs from $.03$ to $.07$). In inferior frontal areas, parcellations on the left had greater spatial separation than parcellations on the right ($t(68) = 2.42$, $p < .05$, Cohen's $d = 0.37$). However, in temporoparietal areas, spatial separation was not significantly different on the left and right ($t(64) = 1.32$, $p > .05$, Cohen's $d = 0.20$).

3.2 Relative locations of AF and EmC parcellations

Figure 1 shows that, on average, the parcellations connected by the AF were somewhat more lateral, posterior and superior relative to the contiguous parcellations connected by the EmC. We compared the locations of the parcellations associated with the two tracts by comparing their centers-of-gravity as shown in Table 1. Table 2 shows the results of paired t-tests for these center-of-gravity locations, and confirms that the AF- and EmC- connected parcellation locations differed in both hemispheres.

3.3 Connectivity

We determined the connectivity of each tract to the anatomical subregions in our designated inferior frontal and temporoparietal areas. Connectivity was defined as the percent of each parcellation falling within an atlas region. Table 3, 4 and Figure 3 display our results for the inferior frontal areas. Table 5, 6 and Figure 4 display our results for the temporoparietal areas.

In the inferior frontal areas, left and right hemispheres displayed similar connectivity patterns. Roughly two-thirds of the AF parcellation occupied pars opercularis and one-third occupied pars triangularis, with less than one percent in pars orbitalis. In contrast, only a small percentage of the EmC parcellation fell within pars opercularis, whereas roughly two-thirds fell within pars triangularis and one-third within pars orbitalis (see Table 3). On the left as compared to the right, the AF showed greater connectivity to pars opercularis and less connectivity to pars triangularis and pars orbitalis. By contrast, the EmC showed increased connectivity to pars opercularis on the right relative to the left. Differences between the proportions of the AF- and EmC-parcellations falling within each of these inferior frontal subregions were significant at $p < .0001$ (Table 4). Although all of the comparisons were statistically robust, individual participants displayed substantial variation in connectivity. This variation is represented graphically in Figure 3.

To fully appreciate the degree of individual variability, we also report the percent of participants showing a connection to each subregion (Table 3). For example, the left AF displayed the most extreme profile: only 3% of participants displayed a connection to pars orbitalis, but all participants displayed a connection to pars opercularis. In general, individual variability was greater for the left hemisphere than the right; and within each hemisphere, individual variability was greater for the AF-connected parcellations than the EmC-connected parcellations.

In temporoparietal areas, left and right hemispheres displayed somewhat different connectivity patterns. For the AF, the portion of the parcellation that fell into the middle and superior temporal gyri was evenly divided between them, although that portion was larger on the left (~50%) than right (~20%). About half to two-thirds of the remaining AF parcellation fell into supramarginal gyrus with 10% or less falling into angular gyrus (Table 5). For the EmC, about half the parcellation fell into superior temporal gyrus in each hemisphere. Whereas on the left nearly one-third of the EmC parcellation occupied the middle temporal gyrus, on the right less than 10% occupied middle temporal gyrus. On the left, the remaining parcellation primarily occupied angular gyrus (about 10%) rather than

supramarginal gyrus (only about 5%), whereas on the right the remaining EmC parcellation was evenly divided between the supramarginal and angular gyri (about 20% each). Overall, compared to the AF, the EmC parcellations fell more into temporal lobe (middle and superior temporal gyri) and less into parietal lobe (supramarginal and angular gyri) (Table 6). The range of variation across individual participants was substantial for both tracts (Figure 4).

To fully appreciate the degree of individual variability, we report the percent of participants showing a connection to each subregion (Table 5). For example, the left EmC displayed connectivity to middle and superior temporal gyri for most participants, but fewer than half the participants displayed any connectivity to angular or supramarginal gyri. In both hemispheres the AF and EmC were connected to the superior temporal gyrus for the greatest number of participants (mean=89.75%), but to the angular gyrus for the smallest number of participants (mean=58.75%).

3.4 Volume lateralization

Whereas connectivity measures the relative distribution of a parcellation across anatomical subregions, in this section we compare the absolute volumes of tracts and parcellations on the left to those on the right. Average tract volumes did not differ significantly in the left and right hemispheres for either the AF, or EmC, however, at the individual level, tracts were often lateralized. In contrast, the average cortical parcellations showed substantial left/right asymmetries, and the direction of these asymmetries depended on both the connecting tract and the specific cortical area. In inferior frontal areas the AF-connected parcellations were right-lateralized, whereas the EmC-connected parcellations were left-lateralized. In temporoparietal areas, the AF-connected parcellations were left-lateralized, whereas the EmC-connected parcellations were right-lateralized. However, we were especially interested in how the temporal and parietal gray matter volumes differed, especially for the AF. The temporal volumes were left-lateralized for the AF, whereas they were bilateral for the EmC. The parietal volumes were right-lateralized for both the AF and EmC (see Table 7). Subsequent analyses focus on these volumes.

3.5 Volume variation based on demographic factors

We were interested in whether the volume lateralization patterns seen in our large heterogeneous group varied by demographically defined subgroups. We therefore characterized the laterality of tract and parcellation volumes as a function of potentially relevant demographic variables (gender, handedness, age, education, and cranial vault).

To test for a potential gender difference in the results, we divided the data into male ($n = 35$) and female ($n = 62$) subsets and used two-sample t-tests to determine whether there were gender differences on laterality measures for tracts, inferior frontal, temporal or parietal volumes. We found only one significant difference in laterality: males displayed a greater tendency toward right-lateralized EmC tract volumes, $t(64) = 2.31, p < .05$, although this would not survive correction for multiple comparisons. Otherwise, lateralization did not differ by gender.

Because of the link between handedness and language lateralization, we ran the same t-tests used for the whole group on the right-handed subgroup ($n = 77$ for AF; $n = 55$ for EmC). The lateralization patterns in the whole group are retained in the right-handed group. The few left-handed and ambidextrous participants, ($n = 13$ for AF; $n = 12$ for EmC), as well as the unbalanced number of right-handers, left-handers, and ambidextrous participants limited the statistical power of direct comparisons among handedness subgroups.

We used stepwise regression with standardized beta weights to determine which of three predictors (age, education and cranial vault) best accounted for variation in volume and laterality. The variables were not completely independent: age was positively correlated with education ($r = .33$, $p < .001$), and negatively correlated with cranial vault ($r = -.26$, $p < .01$). In other words, older participants had more years of education but smaller heads.

For the AF, there was evidence of a leftward shift as a function of age and education. Recall that whole group analyses indicated that the inferior frontal and parietal volumes were right-lateralized and temporal volumes were left-lateralized, but tracts were bilateral. However, individuals often differed from the group (see counts in Table 7). Stepwise regressions revealed patterns in these individual differences. AF-connected inferior frontal parcellation volumes were smaller on the right with increasing age ($R^2 = .071$, $F(1,88) = 7.21$, $p < .01$). In addition, laterality shifted leftward with education (Beta = -0.247 , $F(1,87) = 7.86$, $p < .01$) and rightward with cranial vault (Beta = -0.250 , $F(1,87) = 8.42$, $p < .01$). This is a consistent story. Increases in the positively correlated predictors, age and education, both contributed to left-lateralization, whereas cranial vault, which was negatively correlated to age, predicted the rightward lateralization we found in younger, less-educated participants. The AF-connected temporal volumes were larger on the left with increasing age ($R^2 = .109$, $F(1,89) = 10.9$, $p < .001$); and the right parietal volumes increased with cranial vault ($R^2 = .101$, $F(1,89) = 9.99$, $p < .01$). Again, the story is consistent, older subjects had increased temporal lobe volumes on the left, whereas cranial vault, which was negatively correlated to age, was associated with larger right parietal volumes. AF tract volumes, though not significantly lateralized overall, also showed a leftward shift with education: the left tract volume increased ($R^2 = .056$, $F(1,88) = 5.23$, $p < .05$); and tract laterality shifted left ($R^2 = .059$, $F(1,88) = 5.5$, $p < .05$) with greater education.

For the EmC, there was some evidence of a rightward shift with education, especially for the tract and parietal volume. Recall that in the whole group we found inferior frontal parcellations were left-lateralized and parietal volumes were right-lateralized, but temporal volumes and tracts were not lateralized. However, individuals often differed from the group (Table 7), and stepwise regression revealed patterns in these individual differences. We found a significant decrease in the EmC-connected parietal volumes on the left with education ($R^2 = .06$, $F(1,67) = 4.23$, $p < .05$) and on the right with age ($R^2 = .08$, $F(1,67) = 5.99$, $p < .05$). Laterality shifted rightward with education for both the parietal volume ($R^2 = .11$, $F(1,62) = 7.78$, $p < .01$) and the tract ($R^2 = .098$, $F(1,66) = 7.2$, $p < .01$). Because age and education sometimes had conflicting effects, the story for the EmC is less clear than the story for the AF.

4. Discussion

This paper provides a proof of concept for Bidirectional Iterative Parcellation (BIP). We applied BIP to the problem of characterizing a limited set of anterior and posterior language regions and the dorsal (AF) and ventral (EmC) fibers connecting those regions. These particular termini and tracts provided a strong test of the BIP procedure's ability to separate cortical regions by their connecting tracts. We found good spatial separation between contiguous AF and EmC parcellations even though common cortical seed regions were employed to initiate the procedure. In addition, parcellations showed tract-specific patterns of lateralization, although the tracts themselves did not show strong patterns of lateralization at the group level. The BIP procedure yielded stable parcellation solutions in the majority of cases.

The BIP procedure is iterative, and the number of iterations required to obtain a stable solution was related to several factors but not to the hemisphere or the tract involved. As might be expected, younger subjects, larger initial seed areas and larger final parcellations were associated with a greater number of iterations. This suggests that larger regions of grey matter required more processing. We also observed that more iterations were associated with stable than unstable solutions and among stable solutions, more iterations were associated with less movement in the image data. These results suggest that highly improbable connections were quickly rejected by the procedure.

We found that the contiguous AF and EmC parcellations were well-separated. The AF parcellations were located superiorly, laterally and almost always posteriorly relative to contiguous EmC parcellations. The AF connected mostly in pars opercularis and pars triangularis anteriorly with a larger parietal than temporal component posteriorly. In comparison, the EmC connected mostly in pars triangularis and pars orbitalis anteriorly with a larger temporal than parietal component posteriorly. This is consistent with existing evidence that the connectivity of the two tracts is different within our seed regions (see Saur et al., 2008). In addition, separation was better on the left than right in anterior regions. This finding is consistent with the frequent reports of left anterior connectivity differences for these tracts. We speculate that better segregation of the anterior parcellations on the left might be related to greater functional specialization.

AF-connected parcellations were located posteriorly and superiorly relative to contiguous EmC-connected parcellations, especially on the left. These relative locations were consistent with a graded topographic functional organization in which phonological processing (AF) is posterior and superior; whereas semantic processing (EmC) is anterior and inferior (Saur et al., 2010; Xiang et al., 2010). In addition, we found the AF-connected parcellations were more lateral than the EmC-connected parcellations (Martino et al., 2010; Sarubbo et al., 2013). This medial-lateral difference is partly a side effect of the shape of the brain: for example, the x-coordinates on the surface of the frontal lobe decrease anteriorly as the surface of the brain tapers medially. However, the EmC fibers also appear to terminate more deeply in sulci than the AF fibers [see supplemental material].

Within our chosen seed areas, connectivity findings for the AF and EmC were also largely consistent with the literature. In the inferior frontal areas the AF has been shown previously to connect primarily to pars opercularis and pars triangularis (Saur et al., 2008). In the temporoparietal areas, the primary target of the AF on both the left and right was the supramarginal gyrus, which has been implicated in phonological processing (Parker et al., 2005). Also as predicted, in the inferior frontal areas the EmC connected primarily to pars triangularis and pars orbitalis (Saur et al., 2008, Sarubbo et al., 2013). In the temporoparietal areas the EmC connected primarily to the superior temporal gyrus (Makris and Pandya, 2009). To the best of our knowledge, our finding of significantly right-lateralized connectivity to the angular gyrus for both tracts has not been reported in the literature. Compared to the AF, the EmC was more strongly connected to pars orbitalis anteriorly and the angular gyrus posteriorly. This is consistent with reports that pars orbitalis and angular gyrus display strong resting state connectivity (Xiang et al., 2010), increased functional connectivity during comprehension and semantic tasks (Weiller et al., 2011) and are associated with semantic retrieval (Price, 2010).

There has been some ambiguity, however, regarding the connectivity of the EmC to angular gyrus. In fact, some researchers do not report a connection from angular gyrus at all (Martino et al., 2010; Sarubbo et al., 2013), suggesting anatomical variability in this region. In addition, in an fMRI study that explored the functional correlates of word generation, Beeson et al., (2003) found activation in the left angular gyrus for only about half their participants. We believe that the considerable individual variability we found is consistent with both of these reports. If only about 55% of angular gyri are connected to inferior frontal gyri via the EmC, then a dozen brains available for dissection might not show this connection, or not show it consistently enough to be noted. In addition, in the Beeson et al. (2003) tasks, angular gyrus activation might only occur in about half of participants if the semantic route between angular gyrus and the inferior frontal gyrus only occurred in about half the participants.

Lateralization of language-related structures has been of long standing interest. BIP is a different technique for identifying lateralization than the host of other techniques available, and it is reasonable to expect that results may vary across techniques that tap into different properties of the underlying neurological substrate. Our AF parcellations were right-lateralized anteriorly and in the parietal lobes, but left-lateralized in the temporal lobes. Although our limited set of parcellations likely constitute a subset of the regions in which branches of the AF terminate, our laterality findings for this tract are largely confirmatory of the story emerging from recent literature. In comparison to the AF, less work has been done to characterize lateralization of the EmC, therefore our laterality findings for the EmC are mostly new. We found that EmC parcellations were left-lateralized anteriorly, right-lateralized in the parietal lobes and bilateral in the temporal lobes. However, the current story for these tracts is by no means simple nor do we believe it is complete.

The current information concerning laterality of the AF lacks clarity in part because of the complexity of this tract system. Within the designated seed regions, we confirmed that the volume of connected gray matter was larger on the left for the temporal lobe and on the right for the parietal lobe. We also found that the tract volumes were not significantly lateralized

and that the inferior frontal parcellation was right-lateralized more often than left-lateralized. Interestingly, several researchers have hypothesized that both the AF tract and inferior frontal area may play roles in reasoning and intelligence (see Lebel and Beaulieu, 2009; Vernooij et al., 2007) and both may have long developmental trajectories (Berl et al., 2014; Brauer et al., 2013; Perani et al., 2011). The inferior frontal area may also be involved in vocabulary acquisition (Mårtensson et al., 2012). Consistent with these observations, we found that age and education predicted a leftward shift in laterality of the inferior frontal and temporal volumes and the connecting AF fibers. Based on our results, we speculate that the AF system (or at least parts of it) may continue to mature and become increasingly left-lateralized into late adulthood as both vocabulary and reasoning become more sophisticated (see Ramscar et al., 2014). We remind the reader that age and education were correlated in our dataset. This correlation is probably an artifact of working primarily with a university community for whom there is a fairly direct relationship between age and years of education. The number of middle aged and older adults from outside the university community was very small and tended to be well-educated. Relationships between age and cranial vault are not examined further here because the relationship appears to be study-specific.

Like the AF, the EmC is part of a large complex tract bundle (Martino et al., 2010; Sarubbo et al., 2013). For the limited EmC connections we examined, our laterality findings are mostly new. Within the designated seed regions, we found that the inferior frontal parcellation was left-lateralized and the parietal volume was right-lateralized. Although the temporal and tract volumes had a bilateral distribution on average, most individuals were either left or right-lateralized (Table 7). Stepwise regression suggested that these fibers of the EmC tract and the examined termini become increasingly right-lateralized with greater education. This pattern was less robust than the lateralization patterns associated with the AF and should be replicated.

4.1 Limitations

BIP is limited by the selection of the initial seed and target regions, selection must be sufficiently liberal to capture all connectional endpoints of interest; however, very large targets increase the number of iterations and the resulting time to arrive at a stable solution. Because our goal in this paper was to test the BIP procedure, we chose a limited set of termini and did not attempt to separate the AF or EmC into different branches. This choice may have obscured the tendency of tract volumes to be lateralized. For example, the temporal branch of the AF may be left-lateralized and the parietal branch may be right-lateralized, but because of the choice we made to treat the AF as a unitary tract, we cannot identify those differences in this analysis. We also did not attempt to identify all regions that might be connected by the AF or the EmC. For example, the AF likely connects to premotor areas (Martino et al., 2013), but our choice of initial seeds and targets prevented us from identifying those connections. In addition, we did not explore possible connectivity of either tract to frontal pole, middle frontal gyrus, inferior temporal gyrus, occipital lobe or the superior parietal lobule.

In a minority of participants BIP did not produce a stable solution. The EmC was disproportionately affected by this difficulty, particularly on the right. Parker et al. (2005) reported a similar problem with their tractography results. For their 11 participants, they had some difficulty tracking the EmC on the left but they never successfully tracked it on the right. Much of their difficulty was probably related to their anterior terminus, pars opercularis, which we found was minimally connected to the EmC. Deterministic tractography and nonisotropic voxels likely exacerbated the problem for Parker et al. (2005), but given our own difficulties, we believe other factors must be at work. For example, noise and distortion are especially ubiquitous in the temporal lobe (Binney et al., 2012) and may thus disproportionately affect the reliable tracking of EmC fibers. An examination of Figure 1b and c suggest that the EmC thins as it passes through the operculum, and this thinning was particularly pronounced on the right.

Other limitations of the study reflect difficulties with the resolution of the diffusion weighted images, the state of our knowledge about these tracts, and perhaps the heterogeneous effects of standard space registration. Limited resolution of our diffusion-weighted images may prevent us from distinguishing the EmC from contiguous parallel tracts like the inferior or middle longitudinal fasciculi (see Martino et al., 2013 for similar concerns). Consider, for example, that the temporoparietal parcellations we identified for the EmC were frequently discontinuous; this may imply that we are looking at different branches of the EmC, or even different parallel branches of separate tracts, that are confounded because of the limited resolution of the DWI data. The resolution problem is evident throughout the literature where some large fiber bundles are being parsed into different subdivisions as understanding of white matter anatomy progresses. Even in a five-year span, papers have used different names for what may turn out to be the same underlying tract. Finally, despite our precautions, we are aware that registration to and from standard space is a potential source of inaccuracy. Although our analyses suggest this problem is minimal, registration may affect regional brain volume estimates in heterogeneous ways (Allen et al., 2008). Further detailed analysis in native space could be compared to the standard space results we report here.

4.2 Future Directions

It would be interesting to further subdivide the BIP results for the AF to determine whether a parietal and temporal branch would display tract lateralization or change the lateralization and extent of the inferior frontal parcellations. In addition, following Behrens et al. (2003), the connectivity could be explored in more detail by using classification targets to identify fine-grained details of mutual connectivity between anatomical subregions. Finally, we were intrigued by the finding that the EmC and its parcellations become right-lateralized with education. However, it is unclear which cognitive skills associated with education might drive this finding. In this paper we tested the BIP procedure on a limited set of possible termini for two very complex tract bundles. Having established that the procedure is useful, we hope to apply it to a more complete characterization of these tract bundles and others in future work.

4.3 Conclusion

In general, DWI parcellation is a sensitive technique that provides considerable insight into connectivity that cannot be attained in other ways in living individuals. BIP builds on DWI parcellation to characterize connected pairs of regions with increased specificity. Despite being computationally intensive and having some limitations, we believe that BIP is a sensitive and largely automated technique that can provide insights into the connectional anatomy of the brain. Specifically, within the selected seed regions (but especially for the left anterior inferior frontal gyrus), BIP identified the locations of connected cortical regions in great detail, and these findings matched the extant literature. In addition, the procedure identified complex patterns of laterality that may merit future analysis. BIP has already revealed detailed relationships between connectional architecture and demographic variables, and we believe it is a useful addition to the tools available for evaluating structural networks in the brain.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- We present a novel procedure, bidirectional iterative parcellation (BIP).
- BIP isolates cortical regions by connectivity at both ends of a tract.
- BIP identified expected connectivity for the arcuate and extreme capsule.
- BIP identified differences in lateralization related to demographic factors.

Figure 1.

Initial seed regions shown in (a) axial view, (b) sagittal left, and (c) sagittal right. Inferior frontal seed is tan; temporoparietal seed is olive green. These seed regions are approximate. The real seeds are generated in each subject's space, masked with CSF and checked to make sure they do not cross the sylvian fissure. The smoothed thresholded group average of tracts and parcellations (d, e, f): AF (arcuate fasciculus/superior longitudinal fasciculus)= blue, EmC (extreme capsule fiber system)= red, inferior frontal AF parcellation = cyan, inferior frontal EmC parcellation = yellow, temporoparietal AF parcellation = green, temporoparietal EmC parcellation = orange. (d) axial view of the 8 parcellations (no tracts): note the relative position of each parcellation. (e) sagittal left; (f) sagittal right.

Figure 2.

Illustrative termination masks for the left AF (a,b,c) and left EmC (d,e,f) are shown to clarify the masking strategy. AF=arcuate fasciculus/superior longitudinal fasciculus; EmC=extreme capsule fiber system.

Figure 3.

AF=arcuate fasciculus/superior longitudinal fasciculus; EmC=extreme capsule fiber system. Percent overlap of gray matter parcellations with each of the three anatomical regions, arranged posterior to anterior (p. Operc = pars Opercularis, p. Triang= pars Triangularis, and p. Orb = pars Orbitalis). The median value is represented by a prominent dot. Whiskers represent the 25th and 75th percentiles. + is an outlier.

Figure 4.

AF=arcuate fasciculus/superior longitudinal fasciculus; EmC=extreme capsule fiber system. Connectivity with each of the four anatomical regions, arranged inferior to superior (pMTG = posterior middle temporal gyrus, STG = superior temporal gyrus, SMG = supramarginal gyrus, AnG = angular gyrus). The median value is represented by a prominent dot. Whiskers represent the 25th and 75th percentiles. + is an outlier.

Table 1

Locations of each cortical parcellation, as coordinates for the center-of-gravity

<u>Hem.</u>	<u>Medial-Lateral</u>		<u>Anterior-Posterior</u>		<u>Superior-Inferior</u>	
	<u>AF</u>	<u>EmC</u>	<u>AF</u>	<u>EmC</u>	<u>AF</u>	<u>EmC</u>
Inferior Frontal Gyrus						
L	71	67	70	79	43	36
R	20	22	72	78	43	36
Temporoparietal area						
L	73	69	44	47	45	39
R	17	19	44	45	51	45

Note. AF=arcuate fasciculus/superior longitudinal fasciculus; EmC=extreme capsule fiber system. x/y/z coordinates are mean voxel coordinates in FSL 2mm MNI_152 standard space. Medial-Lateral (x): On the left, larger values are more lateral. On the right, larger values are more medial. Anterior-Posterior (y): Larger values are more anterior. Superior-Inferior (z): Larger values are more superior.

Table 2

Differences in locations of the AF and EmC cortical parcellations

Hem.	Medial-Lateral		Anterior-Posterior		Superior-Inferior	
	t	d	t	d	t	d
Inferior Frontal Gyrus						
L	20.2 ***	2.92	27.1 ***	4.02	32.3 ***	4.60
R	15.4 ***	2.17	22.1 ***	3.35	20.2 ***	3.28
Temporoparietal area						
L	14.9 ***	2.01	2.83 *	0.42	10.3 ***	1.43
R	6.6 ***	0.97	1.26	0.17	7.5 ***	1.23

Note. AF=arcuate fasciculus/superior longitudinal fasciculus; EmC=extreme capsule fiber system. Center-of-gravity coordinates for the cortical parcellations of the two tracts (shown in Table 1) were compared by paired t-tests;

 $p < .0001$;

*
 $p < .01$. The effect size for the location difference along each spatial axis is shown as Cohen's d . Medial-Lateral (x): On the left, larger values are more lateral. On the right, larger values are more medial. Anterior-Posterior (y): Larger values are more anterior. Superior-Inferior (z): Larger values are more superior.

Table 3

Group average percent of each cortical parcellation falling within atlas-defined subregions in the inferior frontal gyrus, mean (SD), paired t-tests and effect size. Percent of participants showing tract termination in each region in the left and right hemisphere.

Tract	Subregion	Group Average Parcellation			Percent of Participants		
		Left hem.	Right hem.	t	d	left	right
AF	p. Operc	63.7 (22.6)	58.0 (18.3)	2.15 [#]	0.27	100%	100%
AF	p. Triang	33.6 (23.3)	39.1 (18.3)	2.05 [#]	0.26	89%	97%
AF	p. Orb	0.03 (0.19)	0.7 (1.9)	3.26 [#]	0.49	3%	24%
EmC	p. Operc	0.4 (0.9)	5.9 (10.1)	4.71 [#]	0.77	22%	59%
EmC	p. Triang	63.3 (16.7)	59.4 (24.0)	1.17	0.19	100%	99%
EmC	p. Orb	35.4 (17.4)	32.8 (25.3)	0.45	0.07	98%	92%

Note: AF=cortical parcellation associated with the arcuate fasciculus/superior longitudinal fasciculus; EmC=cortical parcellation associated with the extreme capsule fiber system. p. Operc=pars opercularis, p. Triang=pars triangularis, p. Orb= pars orbitalis. For each participant, the portions of each parcellation falling within the three subregions sums to 100%. The means presented here do not always sum to exactly 100% because a successful parcellation is not included if the contralateral parcellation failed. Paired t-statistics and effect sizes (Cohen's d) for left – right parcellation size differences.

[#] $p < .05$

Table 4

Statistical comparison of the portions of the AF and EmC parcellations in the atlas-defined inferior frontal gyrus subregions. Paired t-tests and effect size.

Hem	Subregion	Result	t	d
L	pars opercularis	AF larger	25.97***	3.96
L	pars triangularis	EmC larger	9.11***	1.39
L	pars orbitalis	EmC larger	17.68***	2.68
R	pars opercularis	AF larger	21.87***	3.54
R	pars triangularis	EmC larger	5.17***	0.94
R	pars orbitalis	EmC larger	11.04***	1.80

Note: AF=arcuate fasciculus/superior longitudinal fasciculus; EmC=extreme capsule fiber system. Percentages of the AF and EmC parcellations falling within atlas-defined subregions are shown in Table 3. Paired t-statistics and effect sizes (Cohen's d).

 $p < .0001$.

Table 5

Group average percent of each cortical parcellation falling within atlas-defined temporoparietal subregions, mean (SD) paired t-tests and effect size. Percent of participants showing tract termination falling within each region in the left and right hemisphere.

Tract	Subregion	Group Average Parcellation			Percent of Participants		
		Left hem.	Right hem.	t	d	left	right
AF	pMTG	25.8% (20.5)	11.1 (14.8)	5.71***	0.82	90%	62%
AF	STG	26.1 (15.7)	9.8 (13.5)	7.96***	1.11	97%	73%
AF	SMG	41.7 (21.0)	65.5 (24.8)	7.67***	1.03	99%	100%
AF	AnG	4.9 (9.4)	11.8 (13.9)	4.18***	0.58	53%	71%
EmC	pMTG	29.6 (27.5)	5.9 (8.5)	7.15***	1.17	82%	57%
EmC	STG	47.5 (32.1)	49.3 (30.0)	0.38	0.06	95%	94%
EmC	SMG	5.1 (10.4)	21.5 (21.0)	5.72	0.99	29%	75%
EmC	AnG	13.5 (21.0)	21.7 (27.9)	2.29#	0.33	46%	65%

Note: AF=cortical parcellation associated with the arcuate fasciculus/superior longitudinal fasciculus; EmC=cortical parcellation associated with the extreme capsule fiber system. pMTG = posterior middle temporal gyrus, STG = superior temporal gyrus, SMG = supramarginal gyrus, AnG = angular gyrus. For each participant, the portions of each parcellation falling within the four subregions sums to 100%, but see note for Table 3. Paired t-statistics and effect sizes (Cohen's d).

p < .0001;

p < .05.

Table 6

Statistical comparison of the portions of the AF and EmC parcellations in the atlas-defined temporoparietal subregions. Paired t-tests and effect size.

Hem.	Subregion	Result	t	d
L	post. middle temporal gyrus	EmC greater	2.38*	0.33
L	superior temporal gyrus	EmC greater	4.18***	0.66
L	supramarginal gyrus	AF greater	16.73***	2.25
L	angular gyrus	EmC greater	3.54**	0.55
R	post. middle temporal gyrus	AF greater	2.49 [#]	0.42
R	superior temporal gyrus	EmC greater	11.06***	1.66
R	supramarginal gyrus	AF greater	11.94***	1.89
R	angular gyrus	EmC greater	3.06 [#]	0.45

Note: AF=arcuate fasciculus/superior longitudinal fasciculus; EmC=extreme capsule fiber system. Percentages of the AF and EmC parcellations falling within atlas-defined subregions are shown in Table 6. Paired t-statistics and effect sizes (Cohen's d).

 $p < .0001$;

**
 $p < .001$;

[#]
 $p < .05$

Table 7

Statistical comparison of volumes on the right and left. Paired t-tests and effect sizes for volume comparison. Counts of participants with left, bilateral or right volume lateralization.

Tract	Region	Result	t	d	left	bilateral	right
AF	IFG	Right larger	2.21 [#]	0.28	34	5	51
AF	TmpPar	Left larger	2.80 [*]	0.39	56	4	30
AF	temporal	Left larger	5.54 ^{***}	0.77	72	1	18
AF	parietal	Right larger	2.83 [*]	0.37	34	8	49
AF	tract	NS	0.96	0.13	21	36	33
EmC	IFG	Left larger	5.78 ^{***}	0.96	49	6	13
EmC	TmpPar	Right larger	2.08 [#]	0.29	24	4	38
EmC	temporal	NS	0.72	0.09	32	2	35
EmC	parietal	Right larger	3.45 [*]	0.53	17	3	44
EmC	tract	NS	0.80 [#]	0.11	23	13	30

Note: IFG=inferior frontal gyrus, TmpPar=temporoparietal area; AF=arcuate fasciculus/superior longitudinal fasciculus; EmC=extreme capsule fiber system. Paired t-statistics and effect sizes (Cohen's d).

p < .0001;

*
p < .01,

p < .05. Counts of participants with who were left-lateralized ($\delta < -.1$), bilateral (δ between $-.1$ and $.1$), or right-lateralized ($\delta > .1$) for each volume.