Mapping of Functional Areas in the Human Cortex Based on Connectivity through Association Fibers

In the human brain, different regions of the cortex communicate via white matter tracts. Investigation of this connectivity is essential for understanding brain function. It has been shown that trajectories of white matter fiber bundles can be estimated based on orientational information that is obtained from diffusion tensor imaging (DTI). By extrapolating this information, cortical regions associated with a specific white matter tract can be estimated. In this study, we created population-averaged cortical maps of brain connectivity for 4 major association fiber tracts, the corticospinal tract (CST), and commissural fibers. It is shown that these 4 association fibers interconnect all 4 lobes of the hemispheres. Cortical regions that were assigned based on association with the CST and the superior longitudinal fasciculus (SLF) agreed with locations of their known (CST: motor) or putative (SLF: language) functions. The proposed approach can potentially be used for quantitative assessment of the effect of white matter abnormalities on associated cortical regions.

Keywords: Brodmann area, cortical connectivity, diffusion tensor imaging, fiber tracts, tractography, white matter atlas

Introduction

It has been shown that diffusion tensor imaging (DTI) provides orientational information about white matter structures (Moseley et al. 1990; Basser et al. 1994a, 1994b; Makris et al. 1997; Pajevic and Pierpaoli 1999; Catani et al. 2002; Mori et al. 2005). This has led to the technique of DTI tractography (Conturo et al. 1999; Mori et al. 1999; Basser et al. 2000; Poupon et al. 2000; Parker et al. 2002; Wakana et al. 2004), which can faithfully reconstruct cores of prominent white matter tracts by using existing anatomical knowledge as anatomical constraints. The possibility of reconstructing these well-described white matter tracts leads to an interesting question: “Can we identify cortical regions associated with a white matter bundle?” Animal studies using neuroanatomical tracers and targeted lesions provide a fair amount of knowledge about white matter tracts that connect functional brain regions (Carpenter 1976; Nieuwenhuys et al. 1983; Nolte and Angevine 2000). These include various projection fibers (connecting the cortex and other regions of the brains), such as thalamocortical and corticothalamic fibers, corticospinal fibers, and corticopontine fibers, to name a few (Friedman et al. 1986; Jones et al. 1976). The connectivity of fibers associated with the limbic system, such as the fornix, the cingulum, and the stria terminalis, has also been well documented (see e.g., Mesulam et al. 1977; Cavada and Goldman-Rakic 1989; Newman et al. 1996; Paxinos 2004). The connectivity information obtained from these animal studies has been a valuable resource from which to infer human brain connectivity.

One of the unique features of the human brain is the existence of prominent association fiber tracts that interconnect various regions of the cortex. These include the superior and inferior longitudinal fasciculus (SLF and ILF), the superior and inferior fronto-occipital fasciculus (SFO and IFO), and the uncinate fasciculus (UNC). These tracts cannot be identified as discrete fiber bundles in rodent brains and are not well developed in nonhuman primate brains or in human fetal brains (Hermoye et al. 2005; Huang, Zhang, et al. 2006; Huang, Walker, et al. 2006; Mori and Zhang 2006). Consequently, the connected cortical regions and functions of these tracts have not been well characterized. It is, thus, of great interest to use noninvasive DTI tractography to estimate cortical regions that are related to these association fibers.

To use DTI tractography for this purpose, however, there are several difficulties. First, tracking data in individual brains are known to have errors due to noise and partial volume effects. Second, the tracking results are not accurate when image pixels contain complex axonal structures, such as crossing fibers (Tuch et al. 2003). This problem can be reduced by reconstructing only the core of white matter tracts with known trajectories. However, to identify associated cortical regions, the tracking results must be extended to subcortical white matter areas, which most likely consist of a mixture of axons with different destinations.

The purpose of this paper is to map cortical regions related to specific association fibers. These maps are expected to provide a quantitative way to estimate the relationship between the functional regions in the cortex and white matter tracts. To tackle the limitations of tractography, we adopted 2 strategies. First, we normalized tractography results from 28 healthy volunteers and created probabilistic maps to reduce the contribution of random errors due to noise and partial volume effects. Second, a sphere of uncertainty was defined to describe the effect of extrapolating tractography results to cortical regions, based on an assumption that the associated cortex is close to the terminal point of tractography. We used Talairach coordinates as a template (Talairach and Tournoux 1988), which allowed us to relate the identified cortical regions to Brodmann’s map. In this study, associated Brodmann’s areas for the SLF, the ILF, the IFO, and the UNC are reported. In addition to these major association fibers, we also mapped the connectivity of the corticospinal tract (CST) and the corpus callosum.

Method

Subjects
Institutional Review Board approval was obtained for the study, and written, informed consent, including Health Insurance Portability and
Accountability Act (HIPAA) compliance, was obtained from all subjects. Twenty-eight healthy adults (mean 29 ± 7.9 years old; male 17, female 11; all right handed) participated in our study.

**Imaging**

A 1.5T MR unit (Gyroscope NT, Philips Medical Systems) was used. DTI data were acquired using single-shot echo-planar imaging with sensitivity encoding (SENSE), parallel imaging factor, 2.5 (Pruessmann et al. 1999). The imaging matrix was 96 × 96 with a field of view of 240 × 240 mm (nominal in-plane resolution = 2.5 mm), zero-filled to 256 × 256 pixels. Transverse sections of 2.5 mm thickness were acquired parallel to the anterior commissure (AC)-posterior commissure (PC) line. A total of 50–55 sections covered the entire hemisphere and brain stem without gaps. Diffusion weighting was encoded along 30 independent orientations (Jones et al. 1999), and the b value was 700 mm²/s. Five additional images with minimal diffusion weighting (b = 30 mm²/s) were also acquired. The scanning time per dataset was approximately 6 min. To enhance the signal-to-noise ratio, imaging was repeated 3 times.

**Data Processing**

The DTI datasets were transferred to a PC running a Windows platform and were processed using the custom-made software, DtiStudio (H. Jiang and S. Mori, Johns Hopkins University, http://lbam.med.jhmi.edu, and Kennedy Krieger Institute http://mri.kennedykrieger.org) (Jiang et al. 2006). All diffusion-weighted and non-diffusion-weighted images were first realigned by affine transformation using the automated image registration (AIR) program (Woods et al. 1998), in order to minimize Eddy current and potential small bulk motions that occurred during the scans. The 6 elements of the diffusion tensor were calculated for each pixel using multivariate linear fitting (Basser et al. 1994a, 1994b). After diagonalization, 3 eigenvalues and 3 eigenvectors were obtained. For the anisotropy map, fractional anisotropy (FA) was used (Pierpaoli and Basser 1996). The eigenvector associated with the largest eigenvalue was used as an indicator of fiber orientation. We also created averaged diffusion-weighted images (aDWI) by adding all diffusion-weighted images. This image was used to drive image registration.

**Fiber Tracking and Region of Interest (ROI) Drawing Strategy**

For the 3D tract reconstruction, the fiber assignment by the Fiber Assignment by Continuous Tracking (FACT) method (Mori et al. 1999; Xue et al. 1999) was used with an FA threshold of 0.2 and fiber angles of less than 40° between 2 connected pixels. The fiber tracking was also performed by DtiStudio. A multi-ROI approach was used to reconstruct tracts of interest (Conturo et al. 1999; Huang et al. 2004), which exploits existing anatomical knowledge of tract trajectories. Tracking was performed from all pixels inside the brain (brute-force approach), and results that penetrated the manually defined ROIs were assigned to the specific tracts associated with the ROIs. The ROI placement followed the protocols described in our previous paper (Wakana et al. 2007). In this study, we reconstructed and studied 7 white matter tracts: the forceps major (FMA), the forceps minor (FMI), the medial corticospinal tract (mCST), the IFO, the ILF, the SLF, and the UNC.

**Normalization**

We used our stereotaxic white matter atlas in Talairach coordinates (JHU-Talairach atlas) as a template (downloadable from http://lbam.med.jhmi.edu/ or http://mri.kennedykrieger.org/). This template was created by transforming the JHU white matter atlas (Wakana et al. 2004; Mori et al. 2005) into the Talairach coordinate. For the transformation, the brain dimensions (width, height, and length) and the following 5 landmarks were used: 2 landmarks at the AC and PC at the midsagittal level and an additional 3 landmarks at the anterior, superior, and posterior edge of the genu, body, and splenium of the corpus callosum, respectively. These dimensions were transformed to those of the Talairach brain using trilinear interpolation. The atlas contains various DT images, including a non-diffusion-weighted image (b0 image), aDWI (average of all diffusion-weighted images), an FA map, color maps, and a T₁-weighted image. For the normalization of the data from 28 volunteers, a 12-mode affine transformation was used between the 2 aDWDs; one from the JHU-Talairach atlas and the other from the subject. The tractography was performed in the native subject space, and the affine transformation matrix was applied to the tract coordinates.

**Cortical Mapping**

The brain surface was generated from the aDWI of the JHU-Talairach brain using a marching cube algorithm (Schröder et al. 1998). To determine which cortical areas were associated with a specific fiber bundle, a 10-mm diameter sphere was added at the end of each individual tracking result (the end of the tracking served as the center of the sphere). The intersection of the sphere and the brain surface was determined, and the coordinates were recorded as a binary mask (1: within the sphere/0: outside the sphere) in the Talairach coordinates. The binary masks, which are 3D matrices with the same dimension as the JHU-Talairach atlas (246 × 246 × 121), were obtained from the 28 normal subjects, and probabilistic maps were calculated for each tract by simply superimposing the 28 binary masks. In this probabilistic map, a pixel with, for example, a value of 0.5 means: 1) this pixel locates at the surface of the brain defined in the JHU-Talairach atlas and 2) 50% of the normal population (i.e., in 14 subjects out of 28) this pixel would be associated with the tract of interest.

**Results**

Figure 1 shows the results of cortical connectivity maps of white matter tracts, including 4 major association tracts (IFO, ILF, SLF, and UNC), the mCST, and commissural fibers (the FMA and FMI). The data indicate that the 4 association tracts connect all 4 cortical lobes namely, frontal–parietal (SLF), frontal–occipital (IFO), frontal–temporal (UNC), parietal–occipital (SLF), parietal–temporal (SLF, ILF), and occipital–temporal (ILF). The mCST clearly labels the motor cortex, although connectivity of the lateral regions could not be detected. As expected, the symmetric regions of the brain are connected by the FMA and FMI that penetrate the splenium and genu of the corpus callosum, respectively. Figure 2 shows the Talairach coordinates of 3 cortical regions connected with high probability by the SLF. These regions are identified as areas 22 (Wernicke’s area), 44 (Broca’s area), and 40 (supramarginal gyrus). Table 1 lists the cortical regions associated with the 4 association fibers with high probability, together with Brodmann’s areas as read from the Talairach atlas. For the SLF, UNC, and ILF, which are related to the temporal lobe, the left hemisphere consistently shows a higher probability than the right hemisphere, whereas the IFO is more symmetric. This result agrees with our previous report, in which the volumes of reconstructed fibers are significantly higher in the left hemisphere for these 3 association fibers (Wakana et al. 2007). For the SLF, the cortical areas with the highest probability are the areas 3 and 4, which are a part of the somatosensory cortex and motor cortex, respectively. Interestingly, probability in this area is highly symmetric. The rest of the areas are dominated by the language-related areas (areas 20, 21, 40, and 44) with significant dominance in the left hemisphere.

**Discussion**

Because of the imaging resolution of DTI (currently 2.5 mm), tract reconstruction does not reveal cellular-level connectivity information for the brain. However, it is of great interest to investigate cortical areas that are proximal to the terminal of well-known large axonal bundles assuming that these areas are
associated with these bundles (tracts). To address the issue that tracking often terminates before reaching the cortex, we used a sphere of uncertainty and determined the intercept between the sphere and the cortex. Because results in individual subjects may be influenced differently by noise, and especially partial volume effects, we created a population average. The resultant probability maps represent group-averaged coordinates of the cortices reached by fiber tracking, which are influenced by measurement reproducibility, anatomical variability, and registration quality. It is widely known that the cortical areas cannot be accurately registered by affine transformation used in this study. Therefore, the degree of probability strongly reflects variability of cortical anatomy among individuals, and it should not be confused as “connectivity strength.” Tractography results also contain false positives and negatives depending on the complexity of tract architecture. Nonetheless, it is encouraging that our tractography-based cortical mapping of the SLF could identify the 3 major language areas: Wernicke’s area, Broca’s area, and the supramarginal gyrus. Our group-based quantitative results are in line with previous publications (Catani et al. 2002; Mori et al. 2002; Makris et al. 2005; Parker et al. 2005), in which the SLF was found to have several major branches associated with these cortical areas.

The neuroanatomical tracer-based studies have provided a wealth of information on the connectivity between different regions in the monkey brain (Jones and Leavitt 1973; Jones

Figure 1. Probability mapping of cortical areas associated with the CST, IFO, ILF, FMa, FMI, SLF, and UNC. The color represents probability as indicated by the color bar, where "1" indicates 100% reproducibility (all 28 subjects have a connection to the pixel). L and R attached to the abbreviated tract names indicate left and right hemisphere. Abbreviations are: CST: corticospinal tract; FMa: forceps major; FMI: forceps minor; IFO: inferior fronto-occipital fasciculus; SLF: superior longitudinal fasciculus; and UNC: uncinate fasciculus.
1975; Jones et al. 1976; Coulter and Jones 1977; Kaas 2002). In the human brain, however, connectivity has been examined by gross dissection, lesion-degeneration, and myelin histology of the postmortem tissues (Schmahmann and Pandya 2007). With these methods, there is no certainty in identifying one-to-one neural connectivity, and comparisons with animal neuronatology provide the best model to illustrate the observations made in the human brain. Whereas a large body of such evidence suggests that there are more similarities than dissimilarities in the brain connectivity between different species, other studies indicate that certain tracts may be somewhat different (Petrides and Pandya 1999; Schmahmann and Pandya 2007).

One example is the IFO that connects the frontal lobe and occipital lobe. The precise trajectory or even the existence of IFO has been questioned in the human brain because of the erroneous characterization of this tract in earlier studies due to the inclusion of subcallosal fibers (for its history, see Schmahmann and Pandya 2007). The majority of the DTI studies support the traditional view of the connectivity pattern between the frontal lobe and the occipital lobe in humans (Kaas 2002; Wakana et al. 2004; Duffau et al. 2005). Using the probability mapping of cortical areas associated with the IFO, the current study also suggests the presumed extremities of the IFO in the occipital lobe and frontal lobe (Fig. 1).

The SLF, historically regarded as a single bundle and synonymous to arcuate fasciculus (AF) in the human (Dejerine 1895; Catani et al. 2005), has been found to be a collection of 4 tracts comprising SLF-I, SLF-II, SLF-III, and AF (Makris et al. 2005). The latter conceptualization of SLF and AF in humans is in agreement with isotope studies in monkeys (Petrides and Pandya 1984, 1988; Schmahmann and Pandya 2006). These tracts are bidirectional, and the connectivity patterns are similar between the human (Makris et al. 2005) and the monkey (Schmahmann et al. 2007). SLF-I connects the superior parietal lobe (area PE) with the superior frontal lobe (areas 6, SMA, and 9) corresponding to the prefrontal/supplementary motor cortex and prefrontal cortex. SLF-II, considered the major part of SLF, connects the parietal cortex (areas PG and PO) with the frontal eye field (area 8), premotor cortex (area 6), and prefrontal cortex (area 46). SLF-III situates ventrally connecting the inferior parietal lobe (areas PF and PFG) with the premotor and dorsolateral prefrontal cortex (Brodmann’s areas 6, 44, and 46). AF connects the superior temporal gyrus with the frontal eye field (area 8) and dorsal prefrontal cortex (area 46).

In the monkey study, area 9 (prefrontal cortex) has been included in addition to area 46 (prefrontal cortex) as the connection site for SLF, and this subtle difference with the human study appears to arise from the differences in spatial resolution in the methodologies employed in the 2 studies. Makris et al. (2005) have further subgrouped the vertical portion of AF as AFV, interpreting AF more distinct from the rest of the SLF in the human. Future improvements in spatial resolution and cross-fiber separability in DTI images may increase the body of evidence for specific connecting patterns in the human brain.

One unexpected finding is that the SLF has strong and symmetric association with area 4, the motor cortex. Several previous studies have demonstrated that there is a strong connection between the parietal lobe and the premotor cortex (Nieuwenhuys et al. 1983; Catani et al. 2005; Makris et al. 2005; Schmahmann et al. 2007). This SLF-II component may account for the result. It also could be an artifact due to the close proximity of the mCST; this could be a region where the mCST and the SLF are considerably intertwined and a part of the mCST could be mislabeled as the SLF in tractography.

For the rest of the cortical regions associated with the SLF, a strong asymmetry was observed. This could be related to the dominant hemisphere and agrees with previous studies that reported an asymmetry of the SLF (Park et al. 2004; Makris et al. 2005; Nucifora et al. 2005). This left dominance was also found in the tracts related to the temporal lobe; namely, the UNC and the ILF. These findings are also in line with previous publications (Kubicki et al. 2002; Eluvathingal et al. 2007; Wakana et al. 2007). This asymmetry, seen particularly in the area related to the temporal lobe, could be relevant to functional lateralization (Silani et al. 2005; Dorsaint-Pierre et al. 2006). The IFO, which is not related to the temporal lobe, as well as nonassociation fibers (mCST), shows a high degree of asymmetry.

Although the probabilistic approach is expected to reduce the contribution of errors by partial volume effects, it is reasonable to assume that the connectivity maps presented in this study still contain systematic errors. The most apparent example is the result for the mCST, in which only connectivity to the medial regions of the motor cortex is indicated (thus, why we named mCST in this paper). This is attributed to problematic reconstruction areas where the CST and major association bundles cross; in such regions, our tractography map terminates prematurely before the trajectories reach the
Table 1

<table>
<thead>
<tr>
<th>Table of brain regions associated with specific white matter tracts</th>
<th>Left</th>
<th>Right</th>
<th>Brodmann’s area</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ILF</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d(d‘)-E2-5*</td>
<td>0.50</td>
<td>0.20</td>
<td>0.16</td>
</tr>
<tr>
<td>d(d‘)-I-16*</td>
<td>0.50</td>
<td>0.16</td>
<td>0.27</td>
</tr>
<tr>
<td>b(b‘)-I-S*</td>
<td>0.46</td>
<td>0.12</td>
<td>0.63</td>
</tr>
<tr>
<td>c(c‘)-I-6*</td>
<td>0.45</td>
<td>0.16</td>
<td>0.28</td>
</tr>
<tr>
<td>c(c‘)-I-10*</td>
<td>0.44</td>
<td>0.11</td>
<td>0.27</td>
</tr>
<tr>
<td>b(b‘)-H-10</td>
<td>0.41</td>
<td>0.20</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>UNC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c(c‘)-I-10*</td>
<td>0.81</td>
<td>0.19</td>
<td>0.85</td>
</tr>
<tr>
<td>c(c‘)-I-10*</td>
<td>0.79</td>
<td>0.18</td>
<td>0.64</td>
</tr>
<tr>
<td>a(a‘)-A-9</td>
<td>0.73</td>
<td>0.16</td>
<td>0.30</td>
</tr>
<tr>
<td>c(c‘)-I-9*</td>
<td>0.54</td>
<td>0.19</td>
<td>0.63</td>
</tr>
<tr>
<td>b(b‘)-A-9</td>
<td>0.53</td>
<td>0.16</td>
<td>0.27</td>
</tr>
<tr>
<td>c(c‘)-I-10*</td>
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<td>0.05</td>
<td>0.19</td>
</tr>
<tr>
<td>b(b‘)-D-10*</td>
<td>0.48</td>
<td>0.32</td>
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<tr>
<td>b(b‘)-I-8</td>
<td>0.46</td>
<td>0.08</td>
<td>0.25</td>
</tr>
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<td>b(b‘)-B-9*</td>
<td>0.44</td>
<td>0.17</td>
<td>0.43</td>
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<tr>
<td>c(c‘)-I-8*</td>
<td>0.42</td>
<td>0.07</td>
<td>0.11</td>
</tr>
<tr>
<td>c(c‘)-I-11*</td>
<td>0.42</td>
<td>0.34</td>
<td>0.34</td>
</tr>
<tr>
<td>b(b‘)-A-8</td>
<td>0.41</td>
<td>0.09</td>
<td>0.12</td>
</tr>
<tr>
<td>a(a‘)-A-8</td>
<td>0.41</td>
<td>0.15</td>
<td>0.11</td>
</tr>
<tr>
<td>b(b‘)-I-10*</td>
<td>0.40</td>
<td>0.31</td>
<td>0.33</td>
</tr>
</tbody>
</table>

Note: * indicates left side, right side, and no dominance, respectively.

The Talairach coordinates that contain more than 200 pixels with a probability higher than 35% on the left hemisphere are listed. The table entry is sorted based on mean probability value in the left hemisphere.

Numbers indicate mean and standard deviation of probabilities that are calculated for the entire pixel within each Talairach coordinate.

target cortices. Even if the reconstructed fibers could reach cortical areas, their trajectories could still contain errors due to crossing fibers along the pathways. If there are reproducible contributions of the crossing fibers, systematic shifts of target cortical areas may occur. Therefore, it is difficult to establish ground truth from this type of tractography-based connectivity study. In this respect, the tract–cortical association results shown in this paper are mostly confirmatory based on the knowledge-based tractography. If reproducible patterns of the cortical association are found, such results could be used to detect consistent differences between control and patient groups and bring our attention to relevant brain regions. The proposed approach could provide a quantitative means for such initial screening studies. In this respect, we would like to stress that this study is based on our previous multicenter efforts to setup robust protocols for tractography (Wakana et al. 2007). Given the nature of tractography, which is based on pixel-by-pixel water diffusion properties, the results have dependency on adopted algorithms, threshold values, and seed pixel locations. Rigorous and robust tractography protocols are, thus, an essential first step for group-based quantitative studies. The technical framework and the stereotaxic coordinates reported in this paper can be used as a guidance for such studies.

In this study, B0-susceptibility distortion of the DTI images was not corrected, which often plagues the DTI studies based on echo-planar imaging (EPI). Although the distortion was drastically reduced by the employment of the parallel data acquisition, comparison between the anatomical T2-weighted images and b0 images revealed 5–8 mm of distortion along the phase-encoding (anterior–posterior) direction at the temporal pole and the inferior frontal lobe (Huang et al. 2005). The
Talairach coordinates of fibers that involve these regions (i.e., UNC and IFO), therefore, contain this level of inaccuracy in our study.

In conclusion, we demonstrate DTI-based cortical connectivity studies for cortical regions associated with 4 major association fiber tracts, the medial part of the CST and the fiber tracts of the corpus callosum, which were mapped by 3D tract reconstructions. The coordinates of the associated cortical regions were obtained from 28 healthy volunteers and normalized into the Talairach coordinates to generate probabilistic maps. Results from the SLF and the CST agree with previous anatomical studies. This tool may provide a means to quantitatively analyze abnormalities in specific white matter tracts and associated cortical regions.

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Address correspondence to Susumu Mori, PhD, Department of Radiology, Johns Hopkins University School of Medicine, 217 Traylor Building, 720 Rutland Avenue, Baltimore, MD 21205, USA. Email: susumu@mri.jhu.edu.

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