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Microstructural correlations of white matter tracts in the human brain

Michael Wahl [a,b], Yi-Ou Li [a], Joshua Ng [a], Sara C. LaHue [a], Shelly R. Cooper [a], Elliott H. Sherr [b], Pratik Mukherjee [a,c,*]

[a] Department of Radiology and Biomedical Imaging, University of California, San Francisco, CA, USA
[b] Department of Neurology, University of California, San Francisco, CA, USA
[c] Department of Bioengineering and Therapeutic Sciences, University of California, San Francisco, CA, USA

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ABSTRACT

The purpose of this study is to investigate whether specific patterns of correlation exist in diffusion tensor imaging (DTI) parameters across different white matter tracts in the normal human brain, and whether the relative strengths of these putative microstructural correlations might reflect phylogenetic and functional similarities between tracts. We performed quantitative DTI fiber tracking on 44 healthy adult volunteers to obtain tract-based measures of mean diffusivity (MD), fractional anisotropy (FA), axial diffusivity (AD), and radial diffusivity (RD) from four homologous pairs of neocortical association pathways (arcuate fasciculi, inferior fronto-occipital fasciculi, inferior longitudinal fasciculi, and uncinate fasciculi bilaterally), a homologous pair of limbic association pathways (left and right dorsal cingulum bundles), and a homologous pair of cortical–subcortical projection pathways (left and right corticospinal tracts). From the resulting inter-tract correlation matrices, we show that there are statistically significant correlations of DTI parameters between tracts, and that there are statistically significant variations among these inter-tract correlations. Furthermore, we observe that many, but by no means all, of the strongest correlations are between homologous tracts in the left and right hemispheres. Even among homologous pairs of tracts, there are wide variations in the degree of coupling. Finally, we generate a data-driven hierarchical clustering of the fiber pathways based on pairwise FA correlations to demonstrate that the neocortical association pathways tend to group separately from the limbic pathways at trend-level statistical significance, and that the projection pathways of the left and right corticospinal tracts comprise the most distant outgroup with high confidence ($p<0.01$). Hence, specific patterns of microstructural correlation exist between tracts and may reflect phylogenetic and functional similarities between tracts. The study of these microstructural relationships between white matter pathways might aid research on the genetic basis and on the behavioral effects of axonal connectivity, as well as provide a revealing new perspective with which to investigate neurological and psychiatric disorders.

Introduction

Since its introduction over 15 years ago, diffusion tensor imaging (DTI) has enabled the noninvasive assessment of the microstructural organization of human white matter pathways in health and disease (Basser and Pierpaoli, 1996; Pierpaoli et al., 1996). With the more recent advent of quantitative DTI fiber tractography (Conturo et al., 1999; Mori et al., 1999; Basser et al., 2000), it is now possible to reproducibly measure DTI parameters such as mean diffusivity, (MD), fractional anisotropy (FA), axial diffusivity (AD), and radial diffusivity (RD) over the three-dimensional course of many white matter tracts (Wakana et al., 2007). Measurements of DTI parameters from regions of interest within white matter as well as from entire tracts have been shown to correlate with cognitive and other behavioral performance, often with specific microstructure–function relationships in particular white matter tracts (Klingberg et al., 2000; Beaulieu et al., 2005; Tuch et al., 2005; Niogi and McCandliss 2006; Niogi et al., 2008b; Zahr et al., 2009). Decreases in the microstructural integrity of white matter pathways have been found for many neurologic and psychiatric disorders, often correlating with clinical and neurocognitive deficits in these patients (Klingberg et al., 2000; Niogi and McCandliss 2006; Niogi et al., 2008b).

While there has been rapid growth in the understanding of how the microstructural organization of specific white matter pathways correlates with behavior, to our knowledge there has not been a systematic examination of whether quantitative DTI parameters of different tracts co-vary with each other across individuals. The assumption implicit in many DTI studies is that a particular metric such as FA is independent across white matter tracts; hence, each

* Corresponding author. Neuroradiology Section, Department of Radiology and Biomedical Imaging, University of California, San Francisco, 505 Parnassus Avenue, Box 0628, San Francisco, CA 94143-0628, USA. Tel.: +1 415 353 1639; fax: +1 415 353 8593.
E-mail address: pratik@radiology.ucsf.edu (P. Mukherjee).

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pathway is analyzed separately with respect to its contribution to cognitive ability. Conversely, different tracts may be treated as if they were equivalent, such as when measurements in homologous tracts of the left and right hemispheres are averaged or when the contralateral tract is used as a control for the homologous tract ipsilateral to the pathology in clinical studies of disorders presumed to be unilateral. But the precise degree to which microstructural covariances exist between tracts is largely unknown. Several prior studies have reported hemispheric asymmetries in homologous pairs of fiber pathways using DTI in healthy adults (Gong et al., 2005; Powell et al., 2006; Rodrigo et al., 2007), in the developing human brain (Bonekamp et al., 2007; Wilde et al., 2009), and in the aging human brain (Li et al., 2009; Yasmin et al., 2009), but these studies have focused on group differences in the mean value of DTI parameters rather than on assessing their correlation.

The purpose of this study is to investigate whether specific patterns of correlation exist in DTI parameters across white matter tracts in the normal adult human brain, and whether the strength of these putative correlations might reflect phylogenetic and functional similarities between tracts. To this end, we examined tract-based measures of MD, FA, AD, and RD from four pairs of neocortical association pathways (arcuate fasciculi, inferior fronto-occipital fasciculi, inferior longitudinal fasciculi, and uncinate fasciculi bilaterally), a pair of limbic association pathways (bilateral dorsal cingulum bundles), and a pair of cortical–subcortical projection pathways (bilateral corticospinal tracts), following the tract terminology of Mori et al. (2005). From the resulting inter-tract correlation matrices, we investigate whether there are statistically significant correlations of DTI parameters between tracts, and whether there are statistically significant variations among these inter-tract correlations. We specifically examine if correlations between homologous pairs of tracts always exceed those between non-homologous tracts. Finally, we perform a data-driven hierarchical clustering analysis of pairwise DTI correlations to group tracts based on their microstructural relatedness, using the results to test the hypothesis that microstructural correlations reflect phylogenetic and functional similarities between white matter pathways.

Materials and methods

Participants

The inclusion criteria for subjects in this study were healthy volunteers ages 20–50 years. Exclusion criteria included any history of chronic medical illness, neurological or psychiatric disorder, including substance abuse, as well as any contraindications to MR imaging including pregnancy. Any brain morphological abnormalities found on structural MR imaging also constituted an exclusion criterion. Written informed consent was obtained from all participants in accordance with protocols approved by the institutional review board of the University of California, San Francisco. There were a total of 44 subjects (mean age 30.8 ± 7.8 years, 24 men and 20 women, 35 right-handed and 9 left-handed) enrolled who met all inclusion and exclusion criteria.

MRI and DTI acquisition

Magnetic resonance imaging was acquired on a 3 T Signa EXCITE scanner (GE Healthcare, Waukesha, WI) equipped with an 8-channel phased-array head coil. Whole-brain DTI was performed with a multi-slice single-shot spin echo echoplanar pulse sequence (TE = 63 ms, TR = 14 s) using 55 diffusion-encoding directions, isotropically distributed over the surface of a sphere with electrostatic repulsion, acquired at $b = 1000$ s/mm^2, 1 acquisition with $b = 0$ s/mm^2, 72 interleaved axial slices oriented along the anterior commissure–posterior commissure (AC-PC) line, 1.8-mm slice thickness with no gap between slices, a 128×128 matrix and a field of view (FOV) of 230 mm. To reduce echoplanar image distortion, parallel imaging was employed using the Array Spatial Sensitivity Encoding Technique (ASSET) with an acceleration factor of 2. Total acquisition time was 13.07 min. The signal-to-noise ratio (SNR) was in the range of 18–33 on the $b = 0$ s/mm^2 images, as calculated using the difference method that has been shown by Dietrich et al. (2007) to be the most accurate for parallel imaging acquisitions. Higher SNR was found in superficial regions and lower SNR in deeper regions of the brain, reflecting variations in sensitivity of the multichannel phased array head coil.

High-resolution structural 3 T MR imaging was performed using an axial 3D inversion recovery fast spoiled gradient-recalled echo (FSPGR) T1-weighted sequence (TE = 1.5 ms, TR = 6.3 ms, TI = 400 ms, flip angle of 15°) with 230 mm FOV, 156 1.0-mm contiguous partitions at a 256×256 matrix.

DTI processing and tractography

After non-brain tissue was removed using the Brain Extraction Tool (BET; http://www.fmrib.ox.ac.uk/analysis/research/bet/) with a fractional intensity threshold of 0.3 (Smith, 2002), the diffusion-weighted images were corrected for motion and eddy currents using FMRIB's Linear Image Registration Tool (FLIRT; www.fmrib.ox.ac.uk/fsl/flirt) with 12-parameter linear image registration (Jenkinson et al., 2002). All diffusion-weighted images were registered to the unweighted $b = 0$ s/mm^2 image. Images were post-processed offline in DTIstudio v2.4 software (Jiang et al., 2006) using multivariate linear fitting to obtain maps of FA, MD, AD, RD, and directionally-encoded color FA. Tractography was performed with Fiber Assignment by Continuous Tracking (Mori et al., 1999), using the brute-force method in which tracks were seeded from all voxels in the brain with an FA value larger than 0.3. Fibers were tracked while voxel FA values exceeded 0.2 and turning angles of the primary eigenvectors between neighboring voxels were less than 50°. These fiber tracking parameters are similar to other recent quantitative DTI tractography studies of the normal adult brain (Reich et al., 2006; Rodrigo et al., 2007; Wakana et al., 2007; Danielian et al., 2010). Individual tracts were then selected by requiring fibers to pass through manually placed Regions of Interest (ROIs) on DTI color maps, according to protocols specific for each tract, as described by Wakana et al. (2007) and implemented in DTIstudio. Any anatomically implausible fibers were removed using exclusion ROIs, as also described by Wakana et al. (2007). Quantitative tract-based measurements of FA, MD, AD, and RD were obtained for six axonal pathways bilaterally, specifically the arcuate fasciculus (AF), dorsal cingulate bundle (CB), corticospinal tract (CST), inferior fronto-occipital fasciculus (IFO), inferior longitudinal fasciculus (ILF) and uncinate fasciculus (UF). Mid-sagittal projections of the three-dimensional course of the left-sided tracts are illustrated in Fig. 1. Our terminology differs from that of Wakana et al. (2007) in that they refer to the arcuate fasciculus as the "temporal component of the superior longitudinal fasciculus" and they refer to the dorsal cingulum as the "cingulum in the cingulate gyrus part". Since spatial overlap of tracts would influence their microstructural correlation, the degree of overlap was quantified for each tract pair within the same hemisphere in 25 consecutive subjects as the percentage of shared voxels. This is calculated as follows: let V_A be the number of voxels contained within tract A, V_B be the number of voxels within tract B, and V_{AB} be the total number of voxels within tracts A and B where voxels contained within both tracts are counted only once. Then $100\% \times (V_A + V_B - V_{AB}) / (V_A + V_B)$ represents the percentage of shared voxels between tracts A and B.

DTI correlation analysis

The distributions of FA values of each set of p = 12 tracts across the 44 subjects did not differ from normality using the Shapiro–Wilk test, except for FA of the left UF which showed a statistically significant deviation from normality ($p < 0.05$). However, MD values in 8 of the 12