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Genetic influences on brain asymmetry: A DTI study of 374 twins and siblings

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ABSTRACT

Brain asymmetry, or the structural and functional specialization of each brain hemisphere, has fascinated neuroscientists for over a century. Even so, genetic and environmental factors that influence brain asymmetry are largely unknown. Diffusion tensor imaging (DTI) now allows asymmetry to be studied at a microscopic scale by examining differences in fiber characteristics across hemispheres rather than differences in structure shapes and volumes. Here we analyzed 4 Tesla DTI scans from 374 healthy adults, including 60 monozygotic twin pairs, 45 same-sex dizygotic pairs, and 164 mixed-sex DZ twins and their siblings; mean age: 24.4 years ± 1.9 SD). All DTI scans were nonlinearly aligned to a geometrically-symmetric, population-based image template. We computed voxel-wise maps of significant asymmetries (left/right differences) for common diffusion measures that reflect fiber integrity (fractional and geodesic anisotropy; FA, GA and mean diffusivity, MD). In quantitative genetic models computed from all same-sex twin pairs ($N = 210$ subjects), genetic factors accounted for 33% of the variance in asymmetry for the inferior fronto-occipital fasciculus, 37% for the anterior thalamic radiation, and 20% for the forceps major and uncinate fasciculus (all L>R). Shared environmental factors accounted for around 15% of the variance in asymmetry for the cortico-spinal tract (R>L) and about 10% for the forceps minor (L>R). Sex differences in asymmetry (men>women) were significant, and were greatest in regions with prominent FA asymmetries. These maps identify heritable DTI-derived features, and may empower genome-wide searches for genetic polymorphisms that influence brain asymmetry.

Introduction

Asymmetries in brain structure and function have been studied for over a century. Anatomical asymmetries give evidence for the developmental and evolutionary origins of lateralized cognitive functions and behavioral traits, such as language and handedness (Lancaster et al., 2003; Toga and Thompson, 2003; Luders et al., 2005).

Structural brain asymmetries are influenced by both genetic and environmental factors throughout life. The degree of anatomical asymmetry depends to some extent on age (Sowell et al., 2002a), sex (Luders et al., 2003; Witelson et al., 1992), and handedness (Narr et al., 2007).

Aberrant asymmetries, reported in several brain disorders, may indicate a derailment in processes that establish normal hemispheric specialization. Some mental illnesses, such as schizophrenia, are thought by some to arise due to a failure of normal functional lateralization (Crow, 1990; Narr et al., 2007; Hamilton et al., 2007) although such a view is not universally accepted. Altered asymmetries have been found in groups of patients with dyslexia (Beaton, 1997), Williams syndrome (Thompson et al., 2005; Eckert et al., 2006), fetal alcohol syndrome (Sowell et al., 2002b), Huntington's disease (Mühlau et al., 2007), and multiple sclerosis (Koziol et al., 2005). Inherently lateralized pathologies, such as temporal lobe epilepsy (where the seizure focus is typically on one side of the brain only) may also be assessed by mapping the level of brain asymmetry (Lin et al., 2006).

Asymmetries in the rate of disease progression have reported in some, but not all, studies of degenerative diseases such as Alzheimer's disease and mild cognitive impairment (MCI; Thompson et al., 2003; Thompson et al., 1998; Morra et al., 2009). Taken together, all these asymmetries heighten interest in possible differences in the vulnerability of the two hemispheres to various types of neuropathology and age-related decline, and the origins of these differences.

Diffusion tensor imaging (DTI) offers a new opportunity to study hemispheric differences in microscopic fiber characteristics. DTI is a variant of magnetic resonance imaging, sensitive to directionally constrained water diffusion that occurs preferentially along myelinated axons (Basser and Pierpaoli, 1996). The fractional anisotropy (FA) of

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diffusion tends to be higher when fiber tracts are more directionally coherent, or more heavily myelinated, and is a widely accepted index of the microstructural integrity of white matter (Klingberg et al., 2000; Beaulieu, 2002).

DTI studies in twins can be used to determine genetic and environmental effects on fiber architecture. Monozygotic twins share all their genes while dizygotic twins share, on average, half. Estimates of the proportion of variance attributable to genes versus environment may be inferred by fitting structural equation models to data from both types of twins. Twin MRI studies have already found that genetic factors strongly influence several aspects of brain structure, such as cortical thickness, and gray and white matter volumes (Thompson et al., 2001; Styner et al., 2005; Hulshoff Pol et al., 2006; Peper et al., 2007; Schmitt et al., 2008; Chou et al., 2009; Leporé et al., 2008b; Brun et al., 2009). Even so, twin studies using DTI are still quite rare (recent examples include Lee et al., 2009a,b; Kochunov et al., 2010; Chiang et al., 2009b).

Here we used a twin design to map the 3D pattern of asymmetries and to search for regions where these asymmetries are highly heritable. Honing in on heritable DTI-derived signals may empower genome-wide searches for specific contributing genes, by first isolating regions where differences are heritable. This may alleviate, to some degree, the enormous sample sizes and multiple comparisons corrections that frustrate efforts to detect and replicate single-gene effects on brain structure (Stein et al., 2010) and DTI (Chiang et al., 2009b).

We set out to create the first DTI-based maps of asymmetries (left/right hemisphere differences) for commonly-studied fiber characteristics (FA, GA, MD) in a large, mixed-sex twin population ($N = 374$). Studies of fiber-level asymmetries may be confounded by known asymmetries in brain shape, such as the natural petalias that make the right frontal lobe protrude beyond the left (Toga and Thompson, 2003). It makes sense to reduce these pronounced macrostructural differences across subjects before gauging the level of microstructural asymmetry, especially in a mixed-sex population, where sex differences in anatomy may also be found (Brun et al., 2009). We therefore adjusted, as far as possible, for the known structural differences between hemispheres by aligning brains to a "symmetrized" mean deformation target (MDT) created from the set of fractional anisotropy images in the study.

As well as assessing genetic influences on diffusion asymmetry, secondary (exploratory) analyses were also performed to assess any effects of sex and IQ.

Methods

Subjects and image acquisition

Structural and diffusion tensor (DT) whole-brain MRI scans were acquired from 374 subjects with a high magnetic field (4 T) Bruker Medspec MRI scanner. T1-weighted images were acquired with an inversion recovery rapid gradient echo sequence. Acquisition parameters were as follows: TI/TR/TE = 700/1500/3.35 ms; flip angle = 8°; slice thickness = 0.9 mm, with an acquisition matrix of 256 × 256 × 256. Diffusion-weighted images were also acquired using single-shot echo planar imaging with a twice-refocused spin echo sequence to reduce eddy-current induced distortions. Acquisition parameters were optimized to provide the best signal-to-noise ratio for estimation of diffusion tensors (Jones et al., 1999). Imaging parameters were: 23 cm FOV, TR/TE 6090/91.7 ms, with a 128 × 128 acquisition matrix. Each 3D volume consisted of 55 2-mm thick axial slices with no gap and 1.79 × 1.79 mm^2 in-plane resolution. 105 images were acquired per subject: 11 with no diffusion sensitization (i.e., T2-weighted b_0 images) and 94 diffusion-weighted (DW) images ($b = 1149$ s/mm^2) with gradient directions evenly distributed on the hemisphere. Scan time was 14.2 min. The subjects included 120 young adult monozygotic (MZ) twins (60 pairs — 21 males, 39 females), 90 same-sex dizygotic (DZ) twins (45 pairs — 15 males, 30 females); and an additional 164 mixed-sex dizygotic twins (i.e., one male and female twin per pair) and any non-twin siblings for whom scans were available. No subjects reported a history of significant head injury, neurological or psychiatric illness, substance abuse or dependence, or had a first-degree relative with a psychiatric disorder. In addition, all subjects were screened, using a detailed neurocognitive evaluation (de Zubicaray et al., 2008) to exclude cases of pathology known to affect brain structure. In total, diffusion images from 374 (145 males, 229 females) right-handed young adults (mean age: 24.37 years, SD 1.94) were included in this study. Handedness was assessed in these subjects based on 12 items from Annett's Handedness Questionnaire (Annett, 1970).

Preprocessing and general overview

Each subject's T1-weighted MR and DWI images were edited to remove extracerebral tissues. All skull-stripped structural T1-weighted images were linearly aligned (with 9 degrees of freedom) to a standard template to ensure alignment in space. The raw diffusion weighted images were corrected for eddy-current induced distortions using the FSL tool, "eddy_correct". For each subject, the 11 eddy-corrected images with no diffusion sensitization, also called the b_0 images, were averaged. The average b_0 maps were then aligned and elastically registered to the subject's aligned T1-weighted structural scan using a mutual information cost function (Leow et al., 2005) to account for EPI induced susceptibility artifacts. Similar registrations have been shown to be useful for EPI distortion correction (Huang et al., 2008). The rest of the image processing steps, using the distortion corrected sets of diffusion weighted images, are summarized in Fig. 1. A mean deformation template image was created using fractional anisotropy (FA) maps derived from the diffusion-weighted data (detailed below). The FA images were registered directly to the target and the resulting deformation fields were applied to all the anisotropy maps to put them all into the same coordinate space. To further ensure alignment of white matter tracts, the registered FA maps were thresholded to include only those regions where FA > 0.25. These images were then registered to the thresholded template, and the resulting deformation fields were reapplied to all the registered anisotropy maps. Left–right asymmetries in the anisotropy maps were calculated, and various group-wise statistical analyses were performed. Voxel-wise statistics were used, as in many prior DTI studies (Liu et al., 2009; Ardekani et al., 2007). These included quantitative genetic analyses to estimate genetic and environmental contributions to the observed differences. We expected genetic factors to play a substantial role in the lateralization of the fiber anisotropy in language association regions of the temporal lobe, including the arcuate fasciculus (de Jong et al., 2009; Rodrigo et al., 2007). We also predicted that the use of a symmetrized brain template as a registration target might somewhat reduce the level of observed asymmetry, by eliminating factors reflecting brain shape, such as the level of petalia, or torquing, of the brain.

Anisotropy calculation and registration

DTI was introduced by Basser et al. (1994) to characterize the anisotropy (directional preference) in the diffusion of water molecules in brain tissue. In DTI, the MR signal attenuation due to water diffusion in direction k decreases according to the Stejskal–Tanner equation, if a Gaussian distribution is assumed: $S_k(\mathbf{r}) = S_0(\mathbf{r})e^{-b_k D_k(r)}$. Here $S_0(\mathbf{r})$ is the non-diffusion weighted baseline intensity in direction r, $D_k(\mathbf{r})$ is the apparent diffusion coefficient (ADC), and b_k is a constant depending on the direction k. Two of the many popular scalar measures of fiber anisotropy include the fractional anisotropy and geodesic anisotropy. Fractional anisotropy (FA) is one of the most