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Diffusion properties of major white matter tracts in young, typically developing children

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ABSTRACT

Brain development occurs rapidly during the first few years of life involving region-specific changes in both gray matter and white matter. Due to the inherent difficulties in acquiring magnetic resonance imaging data in young children, little is known about the properties of white matter in typically developing toddlers. In the context of an ongoing study of young children with autism spectrum disorder, we collected diffusion-weighted imaging data during natural nocturnal sleep in a sample of young (mean age = 35 months) typically developing male and female (n = 41 and 25, respectively) children. Axial diffusivity, radial diffusivity, mean diffusivity and fractional anisotropy were measured at 99 points along the length of 18 major brain tracts. Influences of hemisphere, age, sex, and handedness were examined. We find that diffusion properties vary significantly along the length of the majority of tracks. We also identify hemispheric and sex differences in diffusion properties in several tracts. Finally, we find the relationship between age and diffusion parameters changes along the tract length illustrating variability in age-related white-matter development at the tract level.

Introduction

Early in life the human brain develops quickly. For example, brain volume expands from approximately 25% of adult size at birth to 75% by 2 years of age and 95% by 6 years of age (Knickmeyer et al., 2008; Pfefferbaum et al., 1994). MRI in children and adolescents has revealed rapid growth in both gray matter and white matter but with considerable regional variability (Giedd et al., 1996; Gilmore et al., 2007, 2012; Huang et al., 2006; Huttenlocher and Dabholkar, 1997; Jernigan et al., 1991; Nordahl et al., 2012; Peterson, 2003; Toga et al., 2006). Multiple factors such as age, sex and hemispheric asymmetry likely contribute to this variability in brain growth (Bonekamp et al., 2007; Eluvathingal et al., 2007; Giedd et al., 1997; Lebel and Beaulieu, 2009; Paus et al., 1999; Schmithorst et al., 2008; Trivedi et al., 2009). Accounting for these factors will produce a more thorough understanding of typical early brain development, which is critical for advancing research in neurodevelopmental disorders (Gabrieli, 2009; Honea et al., 2005; Qiu et al., 2008; Thiebaut de Schotten et al., 2011; Yeatman et al., 2012a).

The inherent difficulties in acquiring magnetic resonance imaging (MRI) data from young children means that relatively little information has been gathered regarding typical brain development prior to 5 years of age. Diffusion-tensor imaging (DTI) allows for detailed exploration of pediatric brain anatomy and has provided important information regarding white-matter development. While most major white matter tracts can be identified at birth, examination of tracts in young children has been somewhat lacking with rare exceptions (Dubois et al., 2006; Hermoye et al., 2006; Huang et al., 2006; Qiu et al., 2013; Trivedi et al., 2009; Weinstein et al., 2010; Wolff et al., 2012; Yap et al., 2011).

White matter tracts consist of thousands of axons entering and exiting at various points to reach specific targets. Thus, using a single diffusion parameter to characterize the entirety of a tract may mask potentially valuable information. To account for this variability and provide a detailed characterization of white matter tract structure during early childhood, we used newly available tractography software (Yeatman et al., 2012b) to analyze 18 white matter tracts in typically developing male and female toddlers ranging in age from 26 to 46 months. We quantified diffusion parameters along the length of each tract and identified localized differences while comparing tract properties between hemispheres and in relation to the age and gender of the subjects. We found substantial within-tract variability in many tracts as well as location specific sexual dimorphisms and differential effects of age on tract diffusion properties.

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Materials and methods

Participants

Participants were recruited through the M.I.N.D (Medical Investigation of Neurodevelopmental Disorders) Institute of the University of California, Davis (UCD), as part of the Autism Phenome Project. Diffusion imaging data were acquired from typically developing children including 41 males and 25 females (Table 1). Participants were recruited as part of a study on autism spectrum disorder, though children with ASD were not included in the present study. Inclusion criteria for the typically developing children included scores within ± 1.5 standard deviations of the mean on all subscales of the Mullen Scales of Early Development. Handedness was assessed by means of behavioral examination. Exclusion criteria were physical contraindications to MRI, diagnosis with a pervasive developmental disorder, specific language impairment or any known developmental, neurological, or behavioral problems. All children were native English speakers. The UCD institutional review board approved this study, and informed consent was obtained from the parent or guardian of each participant.

Imaging procedures

MRI scans were acquired during natural nocturnal sleep at the UC Davis Imaging Research Center using a 3T Siemens Trio whole-body MRI system (Siemens Healthcare, Inc., Erlangen, Germany) equipped with an 8-channel head coil (Invivo, Inc., Gainesville, FL). The scanner room was decorated to be child-friendly with colorful wall hangings, pillows and stuffed animals. Earplugs and/or headphones were used to attenuate scanner noise and children were closely monitored during scanning. This approach has proven highly successful with a success rate of over 85% (Nordahl et al., 2008).

For all participants, images were obtained using a three-dimensional T1-weighted MPRAGE sequence (TR 2170 ms; TE 4.86 ms; matrix 256×256; 192 slices in the sagittal direction, 1.0 mm isotropic voxels, scan time: 8 m 6 s) and a diffusion-weighted, spin echo, echo planar imaging sequence ("ep2d_diff", number of slices: 72, slice thickness: 1.9 mm, slice gap: 0.0, matrix size: 128×128, voxel size: 1.9 mm isotropic, phase encoding direction: anterior to posterior ($A >> P$), phase partial Fourier: 5/8, TR: 11500, TE: 91, scan time: 6 m 56 s), with effective b-value 700 mm^2/s, 30 gradient directions, and five $b = 0$ images acquired at equally spaced intervals over the scan time. T2-weighted images were also obtained for clinical evaluation when possible (i.e. when the child remained asleep). All MPRAGE and available T2 scans were reviewed by a pediatric neuroradiologist and screened for significant, unexpected clinical findings.

Images were acquired from October 2007 to June 2011. In August 2009, the Siemens 3T Trio MRI system was upgraded to a Trio Total Imaging Matrix (TIM) MRI System running version VB15A operating system software. All the VA25A sequences were upgraded and mapped to their corresponding VB15A sequences with no parameter changes having an effect on image quality or appearance, except for the diffusion-weighted sequence. For this sequence, the spatial resolution, b-value, and diffusion gradient directions were preserved, but parameters were changed to reduce the geometric distortion of the images, and the impact of the geometric distortion on the image analysis. Specifically, the phase encoding direction was changed from 'anterior to posterior' ($A >> P$) to 'posterior to anterior' ($P >> A$), to eliminate tissue compression in the anterior temporal and frontal lobes, and the iPAT option (GRAPPA) was used with a factor 2 acceleration to permit shorter TE and reduced effective echo spacing for reduced geometric distortion at all voxels. The phase partial Fourier factor was increased from 5/8 to 6/8 to partially compensate for the factor 2 reduction in data acquired using GRAPPA. The use of GRAPPA allowed TE to be reduced from 91 ms to 81 ms, and echo spacing to be reduced from 0.83 ms to 0.69 ms. It also allowed TR to be reduced from 11,500 ms to 8500 ms, and scan time from 6 m 56 s to 5 m 23 s. Although the diffusion gradient parameters (directions and b-value) were not changed, the reduction in geometric distortion caused averaging (over the local tissue to determine each voxel value) to be different in the pre-upgrade versus post-upgrade images. Thus, there are likely to be differences in the diffusion parameters in regions with reduced geometric distortion. To control for these differences, we included MRI system upgrade status (pre-upgrade, post-upgrade) as a nuisance covariate for all statistical analyses involving diffusion parameters. In the current study, 29 scans (10 females, 20 males) were acquired before the scanner upgrade and 37 scans were acquired (15 females, 22 males) afterwards (Fisher's exact test, $p = 0.62$).

Table 1
Description of participants.

Continuous descriptors	Mean (SD)	Categorical descriptors	N (%)
Age in months	35.28 (4.71)	Left handed	6 (9.09)
Mullen's visual reception t-score	56.23 (11.04)	Right handed	58 (87.88)
Mullen's receptive language t-score	52.92 (7.28)	Undetermined	2 (3.03)
Mullen's expressive language t-score	55.49 (8.73)	Caucasian	51 (77.3)
Mullen's fine-motor t-score	50 (12.68)	Asian	6 (9.1)
		African-American	3 (4.5)
		Pacific-Islander	1 (1.5)
		Other	2 (3.0)
		Not specified	3 (4.5)

Image processing and diffusion tensor calculation

T1-weighted structural image preprocessing follows Nordahl et al. (2011) and included removal of nonbrain tissue using the Oxford Center for Functional MRI of the Brain (FMRIB) brain extraction tool (BET; Smith, 2002) and correction of main field (B0) inhomogeneities using the nonparametric nonuniform-intensity normalization method (N3; Sled et al., 1998). DTI data were processed using the VISTALab (Stanford Vision and Imaging Science and Technology) diffusion MRI software suite. The raw DTI DICOM images were converted to 4-D NifTI format and volumes and motion artifacts were excluded. DTI images were aligned to the motion-corrected mean of the non-diffusion weighted ($b = 0$) images using a rigid body algorithm. DTI images were then resampled to 2-mm isotropic voxels with eddy-current and motion correction using a 7th-order b-spline algorithm based on SPM5. VISTALab image processing software is available as part of the open-source mrDiffusion package available at http://white.stanford.edu/software/.

Diffusion tensors were fitted to the resampled DTI data using a least squares fit and the RESTORE algorithm that also removed outliers from the tensor estimation (Chang et al., 2005). The diffusion tensor model produces measures describing the diffusion characteristics of each voxel. Eigenvalues ($\lambda1$, $\lambda2$, $\lambda3$) from the diffusion tensor are used to compute axial diffusivity ($\lambda1$), radial diffusivity ($\lambda2 + \lambda3)/2$), mean diffusivity ($\lambda1 + \lambda2 + \lambda3)/3$) and fractional anisotropy ($\sqrt{(1/2)}\sqrt{((\lambda1 - \lambda2)^2 + (\lambda2 - \lambda2)^2 + (\lambda3 - \lambda1)^2)} / \sqrt{(\lambda1^2 + \lambda2^2 + \lambda3^2)}$) (Pierpaoli and Basser, 1996). Axial diffusivity (AD) describes diffusion parallel to the principle diffusion direction (i.e. along the long axis of a fascicle of fibers) and has been related to changes in axon integrity such as during axonal degeneration (Kim et al., 2007; Song et al., 2003; Sun et al., 2006; Thomalla et al., 2004). Radial diffusivity (RD) describes diffusion perpendicular to the principle diffusion direction and is decreased with reduced axonal myelination or axon tract density (Song et al., 2002, 2003; Tyszka et al., 2006; Zhang et al., 2009). Mean diffusivity (MD) and fractional anisotropy (FA) are summative measures that describe average total diffusion and a normalized standard deviation of the three diffusion directions, respectively.