NeuroImage 61 (2012) 542–557

Contents lists available at SciVerse ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Quantitative tract-based white matter development from birth to age 2 years

Xiujuan Geng [a,*], Sylvain Gouttard [b], Anuja Sharma [b], Hongbin Gu [a], Martin Styner [a,c], Weili Lin [d,e], Guido Gerig [b], John H. Gilmore [a,e]

[a] Department of Psychiatry, University of North Carolina-Chapel Hill, USA
[b] Department of Computer Science, University of Utah, USA
[c] Department of Computer Science, University of North Carolina-Chapel Hill, USA
[d] Department of Radiology, University of North Carolina-Chapel Hill, USA
[e] Biomedical Research Imaging Center, University of North Carolina-Chapel Hill, USA

ARTICLE INFO

Article history:
Accepted 19 March 2012
Available online 28 March 2012

Keywords:
White matter maturation
Axonal myelination
Early brain development
Diffusion properties
DTI atlas
Fiber tracking
Functional regression analysis

ABSTRACT

Few large-scale studies have been done to characterize the normal human brain white matter growth in the first years of life. We investigated white matter maturation patterns in major fiber pathways in a large cohort of healthy young children from birth to age two using diffusion parameters fractional anisotropy (FA), radial diffusivity (RD) and axial diffusivity (RD). Ten fiber pathways, including commissural, association and projection tracts, were examined with tract-based analysis, providing more detailed and continuous spatial developmental patterns compared to conventional ROI based methods. All DTI data sets were transformed to a population specific atlas with a group-wise longitudinal large deformation diffeomorphic registration approach. Diffusion measurements were analyzed along the major fiber tracts obtained in the atlas space. All fiber bundles show increasing FA values and decreasing radial and axial diffusivities during development in the first 2 years of life. The changing rates of the diffusion indices are faster in the first year than the second year for all tracts. RD and FA show larger percentage changes in the first and second years than AD. The gender effects on the diffusion measures are small. Along different spatial locations of fiber tracts, maturation does not always follow the same speed. Temporal and spatial diffusion changes near cortical regions are in general smaller than changes in central regions. Overall developmental patterns revealed in our study confirm the general rules of white matter maturation. This work shows a promising framework to study and analyze white matter maturation in a tract-based fashion. Compared to most previous studies that are ROI-based, our approach has the potential to discover localized development patterns associated with fiber tracts of interest.

Introduction

Human brain white matter maturation is a complex and long lasting process that begins in the fetal period and continues into adulthood. The most significant period of white matter myelination occurs between midgestation and the second postnatal year (Brody et al., 1987; Yakovlev and Lecours, 1967), and accompanies neuronal synaptogenesis and gray and white matter growth (Glantz et al., 2007; Huttenlocher and Dabholkar, 1997; Knickmeyer et al., 2008). Myelin, the insulating lipid-layers wrapped around axons by oligodendrocytes, is essential for fast impulse propagation. Myelination broadly occurs in two partially overlapping stages in which oligodendroglial proliferation and differentiation is followed by myelin deposition around axons (Knickmeyer et al., 2008). White matter myelination is associated with the development of cognitive functions during the human life span (Brauer et al., 2011; Klingberg et al., 1999; Nagy et al., 2004) and is increasingly recognized as playing a role in neuronal plasticity as well (Bengtsson et al., 2005; Lee et al., 2010). Pruning of exuberant axons, including cell death and axonal retraction, continues throughout white matter development as well (Innocenti and Price, 2005; Luo and O'Leary, 2005). Functional properties such as the compound action potential may also influence the white matter structural development (Drobyshevsky et al., 2005). Characterization of normal white matter growth in early years of life has great clinical relevance and could provide important clues to understanding neurodevelopmental and neuropsychiatric disorders, many of which originate from early disturbances during brain structural and functional maturation (Gilmore et al., 2010).

Previous postmortem studies have shown that CNS myelination follows predictable topographical and chronological sequences with myelination occurring in the proximal pathways before distal pathways, in sensory pathways before motor pathways, in projection pathways before association pathways, in central sites before poles, and in occipital poles before frontotemporal poles (Brody et al., 1987; Flechsig, 1920; Yakovlev and Lecours, 1967). The rapidly emerging field of magnetic

* Corresponding author at: Department of Psychiatry, 229 Medical School Wing B, University of North Carolina, School of Medicine, Chapel Hill, NC 27514, USA.
E-mail address: xiujuan_geng@med.unc.edu (X. Geng).

1053-8119/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
doi:10.1016/j.neuroimage.2012.03.057

resonance imaging (MRI) has made it possible to study white matter maturation in vivo. Conventional structural MRI with T1- and T2-weighted signal intensities reveal similar general spatial and temporal maturation sequences as postmortem observations (Barkovich et al., 1988; Bird et al., 1989; Paus et al., 2001). However these studies rely on signal contrast to infer changes in brain structure or biochemistry, which may not be specific to white matter development (Deoni et al., 2011).

Diffusion tensor MR imaging (DTI) provides substantial insights into white matter pathways in the living brain by measuring water diffusion properties in brain tissue (Basser et al., 1994; Le Bihan et al., 2001). Diffusion anisotropy, such as fractional anisotropy (FA), and apparent diffusion coefficients, such as mean (MD), axial (AD), and radial diffusivity (RD), are common diffusion measurements to characterize fiber structural features. These measurements are possible indicators of axonal organization and degree of myelination (Beaulieu, 2002; Hüppi et al., 1998; Neil et al., 1998; Neil et al., 2002; Song et al., 2002). Evidence from in-vivo and in-vitro studies suggests that anisotropic water diffusion in neural fibers is related to the dense packing of axons and their membranes that hinder water diffusion perpendicular to the long axis of the fibers relative to the parallel direction, whereas myelin may modulate the degree of anisotropy in a given fiber tract (Beaulieu, 2002). Animal studies have shown RD to be better representative of histologic changes in demyelination and dysmyelination models (Budde et al., 2007; Harsan et al., 2006; Song et al., 2003; Zhang et al., 2009). An animal study in rabbits reported that postnatal maturation of the compound action potential (CAP) had a developmental pattern similar to FA, and developmental expansion of immature oligodendrocytes may contribute to structural and functional maturation of white matter fiber tracts before myelination (Drobyshevsky et al., 2005; Wimberger et al., 1995). Diffusion parameters have been shown to provide relevant information reflective of white matter maturation (Hüppi et al., 1998; Lobel et al., 2009; Neil et al., 2002). DTI together with fiber tractography (Conturo et al., 1999; Mori and van Zijl, 2002) has been used in many recent white matter development studies, mainly in childhood and adolescence (Asato et al., 2010; Ding et al., 2008; Lebel et al., 2008; Schmithorst et al., 2002; Snook et al., 2005; Verhoeven et al., 2010). Results show that white matter maturation continues into young adults with increasing FA and decreasing RD.

Although the general pattern of adult myelination is present by the end of the second year and myelination continues at a slower rate into adulthood (Hermoye et al., 2006; Hüppi et al., 1998; Mukherjee et al., 2002; Sampaio and Truwit, 2001; Schneider et al., 2004), few in-vivo large scale studies have been done to characterize the normal axonal growth in early years, especially the first 2 years of life. Studies of premature infants with a small number of healthy neonates for comparison found dramatic myelination and significant gray and white matter volume increases in the peri- and neo-neonatal periods (Haynes et al., 2005; Hüppi et al., 1998; Partridge et al., 2004; Peterson, 2003). Gilmore et al. (2007) showed that maturation of corpus callosum and corticospinal white matter proceeds rapidly in neonatal brains after birth. A study of early white matter maturation focused on one-to-four-month old healthy infants (Dubois et al., 2006, 2008) and revealed that diffusion indices are correlated with age for most but not all fiber tracts. This study classified fiber bundles to different maturation stages where anterior limb internal capsule (ALIC) and cingulum mature slowest, followed by optic radiations, inferior longitudinal and arcuate fascicles, then by spino-thalamic tract and fornix, and the cortico-spinal tract mature fastest. A ROI-based study with three-week to two-year-old infants (Gao et al., 2009a) found consistent spatiotemporal development of white matter with increase in FA and decrease in AD and RD, moreover, the second year change of diffusion indices are more subtle compared to the first year change.

Three main processes are thought to crucially influence diffusion measurement changes during development (Dubois et al., 2006, 2008): 1) fiber organization in fascicles, which would lead to decreased RD and increased AD, and therefore increased FA but relatively unchanged mean diffusivity; 2) the proliferation of glial cell bodies and intracellular compartments (cytoskeleton, etc.), associated with a decrease in RD and AD and unchanged FA; 3) axonal myelin synthesis that would correspond to decreased RD and unchanged AD and therefore increased FA. Since the membrane proliferation and myelin synthesis are two partially overlapped stages and the age interval in our study is about 1 year that may not distinguish cell proliferation and myelin synthesis, we regarded the two developmental processes as one: myelination with decreased RD and AD and increased FA, where the RD change has a larger degree compared to changes in AD and FA. The two maturation processes, fiber organization and axonal myelination, are considered in this current work. We expect that FA would increase and RD would decrease given myelination and organization, and AD would also decrease even the two processes might cause inconsistent changes in AD (Gao et al., 2009a).

The aim of our work was to investigate the white matter developmental pattern as indicated in the diffusion parameters FA, RD, and AD in the major fiber pathways of healthy young children using quantitative tractography. Previous white matter maturation studies in infants less than age two are limited by small sample size, and only examine overall diffusion measurements or measurements on several discrete sites along fiber pathways. In the current work, we collected 295 DTI scans from a large cohort of 211 healthy pediatric subjects after birth, and at ages 1 and 2 years. Ten major white matter pathways including 21 fiber tracts were identified on a population specific DTI atlas built by unbiased group-wise registration (Goodlett et al., 2006, 2009). These major fiber bundles could be tracked more reliably than other tracts with complex structures, such as brain stem and cerebellar tracts due to limitations of infant brain data acquisition. Diffusion indices of FA, radial and axial diffusivities were calculated and statistical analyses were performed along tracts (Corouge et al., 2006; Goodlett et al., 2009). Tract specific spatiotemporal white matter maturation patterns were assessed.

Materials and methods

Subjects

This study was approved by the Institutional Review Board of the University of North Carolina (UNC) School of Medicine. Children analyzed in this work are controls in an ongoing longitudinal study of prenatal and neonatal brain development in children at high risk for neurodevelopmental disorders. Subjects were recruited during the second trimester of pregnancy from the outpatient obstetrics and gynecology clinics at UNC hospitals. Exclusion criteria were the presence of abnormalities on fetal ultrasound or major medical or psychotic illness in the mother. Children who had successful DTI scans were included in this study. Additional exclusion criteria for this analysis included spending >24 h in the neonatal intensive care unit after birth, history of major medical illness, and major abnormality on MRI. After applying the above exclusion criteria, 295 high quality scans are available for 211 children including 163 neonates (2–4 weeks of age), 77 1 year olds, and 55 2 year olds. Demographic information and distribution of scan availability are found in Tables 1 and 2.

Image acquisition and DTI preprocessing

All imaging was performed on a head-only 3 T scanner (Allegra, Siemens Medical Solutions, Erlangen, Germany). All subjects were scanned without sedation. Before neonates were imaged, they were fed, swaddled and fitted with ear protection. Children at 1 and 2 years were mildly sleep deprived (i.e., parents were asked to wake the child 1 h early that day and to skip a nap) before the scan; once asleep they were fitted with earplugs or earphones and placed in the