Int. J. Devl Neuroscience 50 (2016) 26–38

Contents lists available at ScienceDirect

International Journal of Developmental Neuroscience

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

# Development of human white matter fiber pathways: From newborn to adult ages

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ARTICLE INFO

*Article history:*
Received 25 September 2015
Received in revised form 1 February 2016
Accepted 1 February 2016
Available online 15 March 2016

*Keywords:*
Development
White matter
Newborn
Diffusion imaging
Tractography

ABSTRACT

Major long-range white matter pathways (cingulum, fornix, uncinate fasciculus [UF], inferior fronto-occipital fasciculus [IFOF], inferior longitudinal fasciculus [ILF], thalamocortical [TC], and corpus callosal [CC] pathways) were identified in eighty-three healthy humans ranging from newborn to adult ages. We tracked developmental changes using high-angular resolution diffusion MR tractography. Fractional anisotropy (FA), apparent diffusion coefficient, number, length, and volume were measured in pathways in each subject. Newborns had fewer, and more sparse, pathways than those of the older subjects. FA, number, length, and volume of pathways gradually increased with age and reached a plateau between 3 and 5 years of age. Data were further analyzed by normalizing with mean adult values as well as with each subject's whole brain values. Comparing subjects of 3 years old and under to those over 3 years old, the studied pathways showed differential growth patterns. The CC, bilateral cingulum, bilateral TC, and the left IFOF pathways showed significant growth both in volume and length, while the bilateral fornix, bilateral ILF and bilateral UF showed significant growth only in volume. The TC and CC took similar growth patterns with the whole brain. FA values of the cingulum and IFOF, and the length of ILF showed leftward asymmetry. The fornix, ILF and UF occupied decreased space compared to the whole brain during development with higher FA values, likely corresponding to extensive maturation of the pathways compared to the mean whole brain maturation. We believe that the outcome of this study will provide an important database for future reference.



## 1. Introduction

Long-range white matter tracts play different functions by linking various brain regions, and this emergence of normal hemispheric asymmetry of the brain is important to many cognitive functions (Mesulam, 1990; Gazzaniga, 1995; Gotts et al., 2013). It is known that such white matter tracts take different courses of maturation during normal brain development. For example, studies have shown that the last pathways to become myelinated are the frontal and temporal association regions (Kinney et al., 1988). There has been growing awareness of the fact that abnormal white matter development is linked to altered brain connectivity in various neural developmental disorders such as autism, Asperger syndrome, attention deficit hyperactivity disorder (ADHD), idiopathic developmental delays, multiple sclerosis, schizophrenia, sensory processing disorders, and Tourette syndrome (e.g., Nowell et al., 1988; Rapoport et al., 2001; Widjaja et al., 2008; Neuner et al., 2010; Clark et al., 2012; Owen et al., 2013; Roine et al., 2013; Abdel Razek et al., 2014). It is therefore essential to develop a clear picture of the normal patterns and timing of development of brain

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http://dx.doi.org/10.1016/j.ijdevneu.2016.02.002
0736-5748/

pathways to accurately assess and diagnose brain disorders during development.

Abnormal hemispheric asymmetry is also found in many neural developmental disorders such as autism (Chiron et al., 1995) and mental disorders such as depression (Bruder et al., 2012) and schizophrenia (Andreasen et al., 1982). Typical asymmetries in the human brain have been noted through differences in the morphometry of brain surface starting from fetal stages (Hochestetter, 1929; Fontes, 1944; Chi et al., 1977; Heilbroner and Holloway, 1988; Gilmore et al., 2007; Hill et al., 2010; Kasprian et al., 2011) and asymmetric differences in white matter tract pathways in children and adults (Lebel and Beaulieu, 2009). For example, in children (>5 years old) and adults, the right inferior fronto-occipital fasciculus (IFOF) and the left inferior longitudinal fasciculus (ILF) (Thiebaut de Schotten et al., 2011) revealed early lateralized development, suggesting that asymmetry probably emerges in association pathways earlier than 5 years of age. In fact, significant neuroanatomical changes in the cerebral white matter occur even earlier (Provenzale et al., 2007). For example, leftward asymmetry beginning as early as 15 gestational weeks in the ILF was observed in our previous study (Song et al., 2015). However, there is a lack of consensus about detailed spatio-temporal courses of development of connectivity and emerging asymmetry of white matter pathways in the human brain from development to adult ages (Mukherjee et al., 2002; Neil et al., 2002; Huang et al., 2006; Hasan et al., 2009; Gao et al., 2009; Peng et al., 2009; Geng et al., 2012; Peters et al., 2012; Cancelliere et al., 2013).

High-angular resolution diffusion MR imaging (HARDI) tractography enables identification of complex crossing tissue coherence in the brain (Tuch et al., 2003), even in immature fetal brains (Takahashi et al., 2011, 2012), which are typically more challenging to segment due to a surplus of unmyelinated fibers. HARDI tractography allows for the reconstruction of water diffusivity in many different directions in each imaging voxel. This technique, theoretically, provides an advantage over diffusion tensor imaging (DTI) (Frank, 2002; Tournier et al., 2004), because there are many places throughout the brain where white matter tracks cross and going many different directions (Tournier et al., 2007). Although there have been several techniques to assess white matter development without doing diffusion MR tractography (e.g., O'Muircheartaigh et al., 2014; Ball et al., 2013), advantages of diffusion tractography includes the detection of three-dimensional courses of fiber bundles. Many research studies have investigated white matter pathways in adults using diffusion tractography (Chao et al., 2009; Jin et al., 2011; Cercignani et al., 2012; Trojsi et al., 2013; Racine et al., 2014; Thong et al., 2014; Varentsova et al., 2014). However, there have been much fewer studies on the development of pathways from birth to adult ages. A few studies (e.g., Cancelliere et al., 2013; Uda et al., 2015) investigated white matter pathways from infant to adult ages by studying growth curves of pathways, but neglected to study laterality.

The objective of this research study is to investigate significant developmental changes, including emergence of asymmetry, that occur in various major pathways in the brain using HARDI tractography. The white matter tracts identified include projection (thalamocortical [TC]), limbic (cingulum bundle and fornix) and association (uncinate fasciculus [UF], IFOF, IFL, and corpus callosal [CC]) pathways.

Research has shown that the human brain develops significantly during the first few years of life (Thompson, 2001 Lippé et al., 2009; Gredebäck and Kochukhova, 2010; Berchicci et al., 2011), even going as far as saying that the brain of a 3 year old goes through enough developmental changes that it closely resembles that of an adult brain (Howes, 1983; Schimdt and Beauchamp, 1988; Eckerman and Didow, 1989; Berthier et al., 2000; Whiten et al., 2006; Keen and Shutts, 2007; Keitel et al., 2013; Smith et al., 2015). Piaget's stages of cognitive development states that, at the age of 3, the child starts to integrate the use of symbols as his or her language skills, memory skills and imaginative thinking increases in complexity (Berthier et al., 2000; Hood et al., 2000; Keen and Shutts, 2007). This is further supported by the major developmental milestones for a 3 year old checklist provided by the Centers for Disease Control and Prevention, which indicates that increased language skills, communication skills and cognitive abilities are usually seen in children 3 years of age (American Academy of Pediatrics, 2009; Carlson 2005; Schimdt and Beauchamp, 1988; Smith et al., 2015; Williamson et al., 2011; Williamson and Meltzoff, 2011). By the age of 3, most major white matter tracts are well defined while the brain, itself, has gone through rapid myelination and its water content decreased quite significantly (Dobbing and Sands, 1973; Holland et al., 1986; Penn et al., 1980). Lipid content, protein content and cholesterol levels also increase rapidly during the first 3 years (Brant-Zawadzki and Enzmann, 1981; Dobbing and Sands, 1973; Holland et al., 1986). Thus, it is possible to form two groups of subjects, one group filled with those 3 years and younger while the other group is filled with anyone older than 3 years as the 3 years and younger group can be considered "before the first significant brain development" and the plus 3 years old group to be "after the first significant brain development." Therefore, in the current study, we focused on the difference between the two groups: 3 years old and under, and over 3 years old. We believe that t-tests comparing these age groups accounted for the age factor.

## 2. Materials and methods

### 2.1. Subjects and MR imaging acquisition

The Institutional Review Board at Boston Children's Hospital deemed this an exempt project because the research is retrospective and involved existing data with no risk to patient confidentiality. Initially, we selected 90 subjects with our inclusion criteria. These patients had no neurological/psychiatric history and no MRI-based abnormalities. Newborns and infants were scanned during sleep, some with, and some without, sedation. Since this is a retrospective study, detailed information whether or not the subjects were sedated was not available. Regarding subjects' motion, no motion-correction preprocessing was performed, but we obtained the information on the degree of motion, and excluded subjects that moved more than at least 2 mm in one of the three directions (x, y, z). We did not apply motion correction because it sometimes causes erroneous tractography pathways. Seven subjects were excluded based on motion artifacts (four newborns/infants under 1 year old, one 3 years old, one 6 years old, and one 9 years old subjects). The age distribution was as follows: 6 months and under, 10; 6–12 months, 9; 1–3 years, 5; 4–5 years, 7; 6–10 years, 20; 11–15 years, 16; 16–20 years, 13; 21 years and over, 3. For the eighty-three apparently healthy subjects ranging from newborn to 28 years old, we performed T1-weighted MPRAGE imaging, T2-weighted turbo spin-echo imaging, and an isotropic diffusion-weighted spin-echo echo-planar imaging. Thirty diffusion-weighted measurements ($b = 1000\,s/mm^2$) and five non-diffusion-weighted measurements ($b = 0\,s/mm^2$) were acquired on a 3T MR system (Skyra, Siemens Medical Systems, Erlangen. Germany) with TR = 10 s; TE = 88 msec; $\delta = 12.0$ m s; $\Delta = 24.2$ m s; field of view = 22 × 22 cm; matrix size = 128 × 128, iPAT = 2. Spatial resolution was 2 mm isotropic. These parameters have been used in our work previously for in vivo HARDI tractography on newborn clinical data (Xu et al., 2014).