NeuroImage 182 (2018) 207–218

Contents lists available at ScienceDirect

NeuroImage

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

The development of brain white matter microstructure

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ARTICLE INFO

Keywords:
Brain development
Brain MRI
Myelination
White matter
Neuroimaging

ABSTRACT

Throughout infancy, childhood, and adolescence, our brains undergo remarkable changes. Processes including myelination and synaptogenesis occur rapidly across the first 2–3 years of life, and ongoing brain remodeling continues into young adulthood. Studies have sought to characterize the patterns of structural brain development, and early studies predominately relied upon gross anatomical measures of brain structure, morphology, and organization. MRI offers the ability to characterize and quantify a range of microstructural aspects of brain tissue that may be more closely related to fundamental neurodevelopmental processes. Techniques such as diffusion, magnetization transfer, relaxometry, and myelin water imaging provide insight into changing cyto- and myeloarchitecture, neuronal density, and structural connectivity. In this review, we focus on the growing body of literature exploiting these MRI techniques to better understand the microstructural changes that occur in brain white matter during maturation. Our review focuses on studies of normative brain development from birth to early adulthood (~25 years), and places particular emphasis on longitudinal studies and newer techniques that are being used to study microstructural white matter development. All imaging methods demonstrate consistent, rapid microstructural white matter development over the first 3 years of life, suggesting increased myelination and axonal packing. Diffusion studies clearly demonstrate continued white matter maturation during later childhood and adolescence, though the lack of consistent findings in other modalities suggests changes may be mainly due to axonal packing. An emerging literature details differential microstructural development in boys and girls, and connects developmental trajectories to cognitive abilities, behaviour, and/or environmental factors, though the nature of these relationships remains unclear. Future research will need to focus on newer imaging techniques and longitudinal studies to provide more detailed information about microstructural white matter development, particularly in the childhood years.

Introduction

Brain growth

How does the healthy brain change as we learn, play, and grow? From the micro to macro scale, the human brain undergoes remarkable structural changes throughout childhood that lay the critical foundation for long-term cognitive outcomes and mental health. Infancy and early childhood encompass the period of peak brain growth, but brain structure continues to be refined and remodeled throughout childhood, adolescence, and into young adulthood in response to genetics and environmental conditions (Rice and Barone, 2000; Stiles and Jernigan, 2010).

Major white matter tracts including projection and commissural pathways emerge in the fetal brain between 13 and 18 weeks post conception; thalamocortical and association pathways develop later during the fetal period (24–32 weeks) (Huang et al., 2009; Takahashi et al., 2012; Vasung et al., 2017). All major white matter tracts are present by the end of normal gestation (37–42 weeks) and can be identified using diffusion tractography (Jovanov-Milosevic et al., 2006; Keunen et al., 2017), even though little myelin is present. Fetal white matter development involves pre-myelination phases such as proliferation of oligodendrocyte progenitor cells, followed by development of immature oligodendrocytes, and ultimately, development of mature oligodendrocytes, the glia that form the myelin sheath (Jakovcevski et al., 2009).

The elaboration of the myelin sheath around neuronal axons

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https://doi.org/10.1016/j.neuroimage.2017.12.097
Received 9 June 2017; Accepted 30 December 2017
Available online 3 January 2018
1053-8119/

(myelination) begins in mid-to-late gestation (at approximately 20 weeks) and plays an increasing role in brain communication (Fields, 2010). As the lipid myelin sheath forms around the neuronal axons, it acts to increase the conduction velocity of electrical impulses, improving brain connectivity. Myelination advances rapidly throughout early childhood (the first 5 years of life) in a carefully choreographed caudal-cranial, posterior-to-anterior arc (Barkovich et al., 1988; Yakovlev and Lecours, 1967). This ontogenic pattern is tightly regulated by neural activity (Demerens et al., 1996; Ishibashi et al., 2006), and coincides with the emergence of cognitive skills and abilities (Fornari et al., 2007; Luna et al., 2004). While the majority of myelination occurs during the first 2 years of life, this critical process continues through adolescence and adulthood, reaching a maximum in the 2nd or 3rd decade of life (Yakovlev and Lecours, 1967), and undergoes refinements throughout the lifespan.

White matter microstructural development is susceptible to environmental influences and changes can be induced by learning or intense activity (Fields, 2008; Zatorre et al., 2012). A possible mechanism for these changes is activity-dependent myelination, either via new myelination of previously-unmyelinated pathways, or via myelin remodeling of already myelinated axons (Fields, 2015). The exact mechanisms remain unclear, though both animal and human studies show white matter plasticity in response to learning or environmental stimuli that suggest ongoing interactions between brain development and one's environment (Blumenfeld-Katzir et al., 2011; Keller and Just, 2009; Scholz et al., 2009). While plasticity may vary in magnitude and time course, it is not limited to particular developmental periods, but has been shown to occur at all stages of life.

Magnetic resonance imaging

The advancement of non-invasive neuroimaging techniques, particularly magnetic resonance imaging (MRI), has allowed a new generation of investigations into the patterns of brain growth. By selectively 'tuning' the MRI signal via acquisition protocol and parameters, information can be obtained on differing but complementary aspects of the tissue microstructure. The most historical of these measures are the longitudinal and transverse relaxation times (T1 and T2, respectively) (Bottomley et al., 1984). Changes in T1 and T2 can be driven by differences in water, lipid and molecule content, iron concentration, cell packing and density, and other tissue properties that affect water mobility (Gelman et al., 2001; Miot-Noirault et al., 1997). Another method for improving myelin contrast is using the ratio of T1 to T2-weighted imaging (Glasser and Van Essen, 2011). T1 and T2 imaging are sensitive to microstructural features (e.g., myelination, iron, and water content/fibre packing), but are more typically used to measure brain macrostructure including volume, cortical thickness, and surface area.

More commonly, MRI studies assess microstructure using metrics derived from the measurement of water diffusion with diffusion tensor imaging (DTI), including fractional anisotropy (FA) and mean, radial, and axial diffusivity (MD, RD, and AD, respectively). These DTI parameters are sensitive to aspects of tissue microarchitecture such as local fibre density, coherence, orientation, myelination, and overall tissue 'integrity' (Basser and Jones, 2002; Beaulieu, 2002). DTI data also allow reconstruction of the 3D fibre architecture via tractography (Basser et al., 2000; Mori et al., 1999). Animal models confirm the sensitivity of DTI measures to myelin in single and coherent fibre systems (e.g., spinal cord, corpus callosum) (Song et al., 2002, 2003), but also show that anisotropy is present in the absence of myelin (Beaulieu, 2002; Beaulieu and Allen, 1994). DTI has been by far the most widely used technique to assess development of tissue microstructure, likely because of quick scan times that can be tolerated by children, convenient access to protocols on clinical scanners, and the availability of free, user-friendly analysis software.

However, DTI is limited, particularly in areas with multiple fiber populations where the tensor model is insufficient, which may be the majority of the brain (Jeurissen et al., 2013). A variety of alternate diffusion acquisition schemes and models have been introduced to overcome the limitations of DTI, though most have not yet found wide application in neurodevelopment. Acquisition techniques such as high angular resolution diffusion imaging (HARDI)(Tuch et al., 2002) and diffusion spectrum imaging (DSI)(Wedeen et al., 2005) collect more directions than DTI and use higher b-values (Tournier et al., 2013). This enables more complex models fitting multiple fiber orientations in each voxel to better reflect tissue microstructure. Alternatively, models have been developed to characterize white matter microstructure in more detail than DTI parameters. These include the composite hindered and restricted CHARMED model (Assaf and Basser, 2005) and neurite orientation dispersion and density imaging (NODDI) (Zhang et al., 2012), which provide additional architectural information, including axonal and neurite density (NDI) and orientation dispersion index (ODI). Diffusion kurtosis imaging (DKI) is a model-free fitting that measures deviations from the Gaussian signal caused by restricted diffusion (Jensen et al., 2005). Its parameters are analogous to those from DTI, with mean, axial, and radial kurtosis (MK, AK, RK). White matter tract integrity (WMTI) is an extension of DKI that relates measures to microstructure, providing estimates of intra-axonal water fraction and fiber dispersion (Fieremans et al., 2011). Fixel-based analysis (FBA) is new technique that provides measurements of specific fiber populations within a voxel (Raffelt et al., 2015), overcoming some of the averaging limitations of DTI metrics. These more advanced acquisitions and models often require double or triple the scan time of a typical DTI acquisition, meaning that fewer children will be able to tolerate the scan and provide good data, and making them less attractive to researchers attempting to acquire additional data (e.g., functional MRI) within the same study. Furthermore, analysis is not as straightforward and software not as readily available for advanced diffusion techniques as it is for DTI. Thus, while these advanced acquisitions and models are capable of providing valuable information, they have not been as extensively used to study neurodevelopment, particularly beyond infancy.

Magnetization transfer (MT) imaging utilizes off-resonant prepulses ($+\Delta$ or $-\Delta$) that saturate the macromolecular protons, which then exchange with the free-water protons, reducing the signal available for imaging (Henkelman et al., 2001). Magnetization transfer ratio (MTR) is the ratio of a reference signal to that obtained with the off-resonant pulse, and provides a measure sensitive to macromolecular content, including myelin. Quantitative magnetization transfer (qMT) is a related measure that requires longer acquisition times but more accurately quantifies the macromolecule-bound water fraction than MTR, and also provides an indirect measure of myelin content (van Buchem et al., 2001). MTR and qMT both show strong associations with myelin content in postmortem studies (Schmierer et al., 2004, 2007, 2008). An extension of MT is inhomogeneous MT (ihMT) (Varma et al., 2015), which exploits a difference between the positive and negative offset signal to improve the sensitivity and selectivity to lipid (e.g., myelin) protons. ihMT contrast within brain white matter is driven by dipolar coupling in lipid membranes of myelin (Manning et al., 2017). Chemical exchange saturation transfer (CEST) approaches including amide proton transfer (APT) imaging (Zhou et al., 2003) also offer contrast mechanisms based on interactions between macromolecular and water protons that may useful for assessing microstructural brain development.

Improved sensitivity to myelin and myeloarchitecture can also be achieved via multi-component relaxation time measurement. Here, the measured MRI signal is assumed to result from multiple water species, each with distinct T1 and T2 properties (MacKay et al., 2006). With sufficient measurements and appropriate modeling, it is possible to decompose the measured signal into these individual contributions. Analysis of spine and brain tissue has consistently revealed the presence of at least two distinct water pools with fast and slow relaxation times that through disease and histological studies have been ascribed to water trapped within the lipid bilayers of the myelin sheath, and the less-restricted intra and extra-cellular water, respectively (Laule et al.,