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Neurite density index is sensitive to age related differences in the developing brain

Sila Genc[a,b,*,1], Charles B. Malpas[a,c,1], Scott K. Holland[d], Richard Beare[a,e], Timothy J. Silk[a,b]

[a] Murdoch Childrens Research Institute, Melbourne, Australia
[b] Department of Paediatrics, University of Melbourne, Melbourne, Australia
[c] Department of Medical Education, Melbourne Medical School, The University of Melbourne, Melbourne, Australia
[d] Department of Radiology, Cincinnati Children's Hospital Research Foundation, University of Cincinnati, OH, USA
[e] Department of Medicine, Monash University, Melbourne, Australia

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ABSTRACT

Purpose: White matter development during childhood and adolescence is characterised by increasing white matter coherence and organisation. Commonly used scalar metrics, such as fractional anisotropy (FA), are sensitive to multiple mechanisms of white matter change and therefore unable to distinguish between mechanisms that change during development. We investigate the relationship between age and neurite density index (NDI) from neurite orientation dispersion and density imaging (NODDI), and the age-classification accuracy of NDI compared with FA, in a developmental cohort.

Method: Diffusion-weighted imaging data from 72 children and adolescents between the ages of 4–19 was collected (M=10.42, SD=3.99, 36 male). We compared NODDI metrics against conventional DTI metrics (fractional anisotropy [FA], mean diffusivity [MD], axial diffusivity [AD] and radial diffusivity [RD]) in terms of their relationship to age. An ROC analysis was also performed to assess the ability of each metric to classify older and younger participants.

Results: NDI exhibited a stronger relationship with age (median R^2=.60) compared with MD (median R^2=.39), FA (median R^2=.27), AD (median R^2=.14), and RD (median R^2=.35) in a high proportion of white matter tracts. When participants were divided into an older and younger group, NDI achieved the best classification (median area under the curve [AUC]=.89), followed by MD (median AUC=.81), FA (median AUC=.80), RD (median AUC=.81), and AD (median AUC=.64).

Conclusion: Our results demonstrate the sensitivity of NDI to age-related differences in white matter microstructural organisation over development. Importantly, NDI is more sensitive to such developmental changes compared to commonly used DTI metrics. This knowledge provides justification for implementing NODDI metrics in developmental studies.

Introduction

Brain maturation across childhood and adolescence is one of the most dynamic and important periods in the development of the brain (Paus et al., 1999; Sowell et al., 2003). Understanding typical development of the brain in children and adolescents, when, where and why maturational changes occur is important for a better understanding of the localization, connectivity and maturation of brain function, cognition, and behavior. This understanding also establishes a baseline from which to reveal when and how neurodevelopmental processes go awry.

A number of neuroimaging studies have sought to characterise the cortical grey matter changes over development (Giedd et al., 1999; Wierenga et al., 2014). White matter volume has consistently been shown to increase throughout adolescence and into adulthood but little is known about the underlying microstructural processes causing this volume change or the relationship with function. Magnetic Resonance

Abbreviations: ATR, Anterior thalamic radiation; AD, axial diffusivity; CCG, cingulum cingulate gyrus; CH, cingulum hippocampus; CST, corticospinal tract; DTI, diffusion tensor imaging; FA, fractional anisotropy; IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; NDI, neurite density index; ODI, orientation dispersion index; RD, radial diffusivity; SLFt, superior longitudinal fasciculus temporal; SLF, superior longitudinal fasciculus; UF, uncinate fasciculus

* Correspondence to: Murdoch Childrens Research Institute, The Royal Children's Hospital, Flemington Road, Parkville, VIC 3052, Australia.
E-mail addresses: sila.genc@mcri.edu.au (S. Genc), charles.malpas@mcri.edu.au (C.B. Malpas), Scott.Holland@cchmc.org (S.K. Holland), richard.beare@mcri.edu.au (R. Beare), tim.silk@mcri.edu.au (T.J. Silk).

[1] Both authors contributed equally to this manuscript.

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Imaging (MRI) techniques such as diffusion-weighted imaging (DWI) provide the ability to indirectly examine the microstructural components of white matter, with age-related changes in diffusion metrics thought to relate to neurobiological processes including myelination and axonal organization (Beaulieu, 2002; Paus, 2010).

The tensor model is most commonly used to derive white matter microstructure metrics including fractional anisotropy (FA), mean, axial and radial diffusivity (MD, AD and RD) (Basser and Pierpaoli, 1996; Mori and Zhang, 2006). FA, the most frequently used measure, has been shown to increase over childhood and adolescence (Lebel et al., 2008, 2012; Simmonds et al., 2014). This increase of FA with age is typically attributed to increased myelination as the white matter matures, however FA is a relatively non-specific metric, and can also be influenced by white matter organisation, axonal density, as well as both intra- and extra-cellular mechanisms (Beaulieu, 2009). The recently developed neurite orientation dispersion density imaging (NODDI) is a multi-compartment model of white matter microstructure, and models the biophysical properties of white matter (Zhang et al., 2012). It offers orientation dispersion index (ODI) and neurite density index (NDI) as alternative metrics to FA. These two indices aim to better quantify, and disentangle, neurite morphology in the brain. ODI models the intra-neurite space (between axons) to characterise angular variation of neurites as well as cell membranes, somas and glial cells that influence the extra-neurite (extracellular) space. NDI models intra-neurite space and characterises density of neurites by restricted diffusion (Sepehrband et al., 2015). Being a more sophisticated model of underlying neurobiology, these measures might reveal more about the developing brain.

Given the relatively recent development of this technique, few studies have investigated NODDI metrics over development. Chang et al. (2015) revealed that across the lifespan, from childhood to late adulthood, there is a strong relationship between NDI and chronological age, compared with FA. Other studies have investigated the relationship between NDI and pre-term birth (Kelly et al., 2016), early development (Jelescu et al., 2015), and ageing in adulthood (Kodiweera et al., 2016; Merluzzi et al., 2016), but have not directly compared NODDI and DTI metrics.

Here we investigate the relationship between DTI and NODDI metrics over white matter development in 72 children and adolescents between 4 and 19 years of age. The main aims of this study were to: (1) model age-related differences in diffusion metrics in development; and (2) compare the sensitivity and specificity of NDI and ODI against DTI metrics over age using an ROC analysis.

Methods

Participants

Participant demographic and imaging data were obtained from the Cincinnati MR Imaging of NeuroDevelopment (C-MIND) Data Repository. Full description of the recruitment process is detailed online (https://cmind.research.cchmc.org/) (Holland et al., 2015). Briefly, informed consent was received from the parent or guardian of children between 4 and 17 years of age, and from adolescents that were 18 years of age. Additionally, assent of children between 5 and 17 was obtained. All procedures were completed in accordance with the Declaration of Helsinki. A total of 72 participants between the ages of 4–19 with multi-shell DWI data were included for analysis in this study (M=10.42, SD=3.99, 36 male).

MRI acquisition

Participants underwent MRI at 3.0 T (Phillips Acheiva TX) with a 32-channel head coil at a single site, the Cincinnati Children's Hospital Medical Center. Full details can be found at https://cmind.research.cchmc.org/. In brief, diffusion-weighted images were obtained with a spatial resolution of 2.0×2.0×2.0 mm, Field of view (FoV): 224×224×120, acquisition matrix: 112×109, bandwidth: 1752.6 Hz, 60 slices, Flip angle: 90°, 61 directions. In addition, 7 images with no diffusion weighting were collected (interleaved b=0 s/mm^2).

Two DWI shells were acquired, one b=1000 s/mm^2 shell (relaxation time/echo time [TR/TE]: 6614/81 ms) and one b=3000 s/mm^2 shell ([TR/TE]: 8112/104 ms). For both shell acquisitions, the gradient tables were constructed using the optimal approach by Cook et al. (2007), which optimises the ordering of gradient directions in DWI so that partial scans have the best spherical coverage.

Image processing and template creation

DWI data were run through the *DTIPrep* Quality Control Tool (http://www.nitrc.org/projects/dtiprep), which is an automatic pipeline that removes diffusion directions below a threshold of acceptable motion and signal loss, and corrects for head motion and eddy current artefact. After quality control, on average 57 diffusion-weighted directions were kept for the b=1000 s/mm^2 shell data (range: [38, 61]), and 55 directions kept for the b=3000 s/mm^2 shell data (range: [39, 61]).

DTI-TK (Zhang et al., 2006) was used to create an unbiased population-based template that uses both the average diffusion features (e.g. diffusivities and anisotropy) as well as the anatomical shape features (such as tract size) in the population. For this step, the low b-value shell was corrected for eddy current distortions and motion artefacts using the tool *eddy_correct* in the Functional Magnetic Resonance Imaging of the Brain (FMRIB) group's software library (FSL: 5.0.8) (Smith et al., 2004). The *dtifit* tool in FSL was then used to generate eigenvalue and eigenvector maps for each participant, and converted to a single volume in DTI-TK format. An initial population specific template was bootstrapped using the IXI aging template (Zhang et al., 2010) followed by affine and deformable alignment, and finally resampled to 1 mm^3 isotropic resolution.

Scalar map generation

Each participant's tensor volume was registered to the population-based tensor template using diffeomorphic alignments. Subsequently, scalar DTI maps (FA, MD, AD and RD) were generated from each normalised tensor map using *TVtool* in DTI-TK.

Data were prepared for NODDI fitting by registering the b=3000 s/mm^2 shell to the b=1000 s/mm^2 shell using FMRIB's Linear Registration Tool (FLIRT) in FSL (Jenkinson and Smith, 2001). The two shells were then merged, and subsequently corrected for eddy current distortions and motion artefacts as above. In order to account for the different TE/TR between the shells, each shell was divided by its respective b0 image as per the developer's recommendation (Counsell et al., 2014) and in line with previous studies that have used this correction method (Kelly et al., 2016; Owen et al., 2014). These DWI data were then converted to a NODDI compatible format, NODDI fitting was performed with a Watson distribution (Zhang et al., 2011), and the output was converted to volumetric parametric maps for NDI and ODI. All NDI and ODI outputs were verified by inspecting the error code file to ensure no errors occurred during the fitting process. NODDI maps including NDI and ODI were registered to the population-based template using the *deformationScalarVolume* tool in DTI-TK. Representative normalised parameter maps from three participants are shown in Fig. 1.

Region of interest generation

An atlas-based region of interest (ROI) analysis was employed using the JHU white matter tractography atlas (Wakana et al., 2005) thresholded at 25%. This atlas comprises 20 white matter tracts (Fig. 2a): bilateral anterior thalamic radiation (ATR), cingulum cingu-