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Cerebral maturation in the early preterm period—A magnetization transfer and diffusion tensor imaging study using voxel-based analysis

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ABSTRACT

The magnetization transfer ratio (MTR) and diffusion tensor imaging (DTI) correlates of early brain development were examined in cohort of 18 very preterm neonates (27–31 gestational weeks) presenting with normal radiological findings scanned within 2 weeks after birth (28–32 gestational weeks). A combination of non-linear image registration, tissue segmentation, and voxel-wise regression was used to map the age dependent changes in MTR and DTI-derived parameters in 3D across the brain based on the cross-sectional *in vivo* preterm data. The regression coefficient maps obtained differed between brain regions and between the different quantitative MRI indices. Significant linear increases as well as decreases in MTR and DTI-derived parameters were observed throughout the preterm brain. In particular, the lamination pattern in the cerebral wall was evident on parametric and regression coefficient maps. The frontal white matter area (subplate and intermediate zone) demonstrated a linear decrease in MTR. While the intermediate zone showed an unexpected decrease in fractional anisotropy (FA) with age, with this decrease (and the increase in mean diffusivity (MD)) driven primarily by an increase in radial diffusivity (RD) values, the subplate showed no change in FA (and an increase in MD). The latter was the result of a concomitant similar increase in axial diffusivity (AD) and RD values. Interpreting the *in vivo* results in terms of available histological data, we present a biophysical model that describes the relation between various microstructural changes measured by complementary quantitative methods available on clinical scanners and a range of maturational processes in brain tissue.

Introduction

During the second and third trimesters of pregnancy, a sequence of maturation events establish the foundations for normal brain structure and function including neuronal proliferation and migration, the formation of axonal pathways, programmed cell death and, toward the end of gestation, myelination (Volpe, 2008). These events proceed within laminarly arranged cellular zones, not found in the adult brain, which set the stage for development through to adulthood (Haynes et al., 2005; Kostovic et al., 2002; Rados et al., 2006). This transient laminar organization develops during the mid-fetal period (17–24 gestational weeks) and attains its developmental peak during the early preterm period (26–34 gestational weeks) between 29 and 32 weeks gestational weeks. It consists of (from pia to ventricle): (a) a marginal zone (MZ), (b) the cortical plate (CP) with high cell-packing density, (c) the subplate (SP) zone, the most prominent zone rich in hydrophilic extracellular matrix (ECM) and subplate neurons, and the location of accumulation of 'waiting' thalamic afferent axons, (d) the intermediate zone (IZ; future white matter (WM)), containing migratory neurons, immature glial cells, large bundles of growing axons and their periventricular crossroads, (e) the subventricular zone (SVZ), a (callosal) fiber-rich zone and (f) the ventricular zone. The developing connections of thalamocortical axons, with their synaptic engagement in the CP after the 'waiting' period in the transient SP zone, followed by the similarly developing connections of the long association axons are the main connectivity events in the brain in the late fetal (22–25 gestational weeks) and early preterm (26–34 gestational weeks)

Abbreviations: ACR, Anterior corona radiata; AD, Axial diffusivity; ALIC, Anterior limb of the internal capsule; CP, Cortical plate; DTI, Diffusion tensor imaging; EC, External capsule; ECM, Extracellular matrix; FA, Fractional anisotropy; FDR, False discovery rate; gCC, Genu of the corpus callosum; GM, Gray matter; GP, Globus pallidus; ILF, Inferior longitudinal fasciculus; IZ, Intermediate zone; MD, Mean diffusivity; MTI, Magnetization transfer imaging; MTR, Magnetization transfer ratio; MZ, Marginal zone; OR, Optic radiation; PLIC, Posterior limb of the internal capsule; RD, Radial diffusivity; sCC, Splenium of the corpus callosum; SFO, Superior fronto-occipital fasciculus; SLF, Superior longitudinal fasciculus; SP, Subplate; SS, Sagittal stratum; SVZ, Subventricular zone; VLN, Ventolateral thalamic nucleus; WM, White matter.

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periods. These events are accompanied by a gradual decrease in the SP thickness. Established earlier, the radial glial system is organized in fascicles of fibers traversing the cerebral wall radially and facilitating the proliferation and migration of cortical neurons and glial cells, such as astrocytes and oligodendrocytes (Gadisseux et al., 1989; Rakic, 2003).

All layers but the MZ are visible on *in vitro* and *in vivo* MRI (Brisse et al., 1997; Girard et al., 1995; Huang et al., 2006; Maas et al., 2004; Rados et al., 2006). The decrease in thickness and increase in signal intensity (on structural T_1-weighted images) of the SP towards the end of the early preterm period is a prominent feature of cerebral MRI in preterm infants and is closely linked to the normal development of axonal connectivity in the brain (Kostovic and Judas, 2002). In the SVZ and IZ, the decrease in T_1-weighted signal during the preterm period has been shown to correspond with areas of migrating radial glial cells (Battin et al., 1998; Childs et al., 1998) and developing crossing axonal pathways (Kostovic and Jovanov-Milosevic, 2006). Using tractography, recent diffusion tensor imaging (DTI) postmortem studies of the human fetal brain have successfully identified immature axonal pathways as early as the beginning of the mid-fetal period (Huang et al., 2006, 2009; Takahashi et al., 2012; Vasung et al., 2010). Furthermore, using these methods, predominant radial coherent pathways crossing the cerebral wall, originating possibly from radial glial fascicles, columns of migrating neurons and/or afferent immature axons, have been described in the mid/late fetal period (17–25 gestational weeks) (Takahashi et al., 2012; Xu et al., 2014). Nevertheless, application of these methods, in particular high angular resolution diffusion imaging (HARDI), to *in vivo* fetal and preterm imaging is limited by subject motion, small brain size and the long duration of scan (above 2 h) required for achieving high-resolution and high signal-to-noise-ratio anatomical images of the developing cerebral architecture. Furthermore, the information gained is related to tissue organization only.

Imaging early preterm neonates at birth gives a unique opportunity to investigate cerebral development and monitor dynamic maturational events *in vivo*. DTI is a powerful method for investigating maturation of WM tracts in the developing brain (Berman et al., 2005; Dubois et al., 2006, 2008; Hermoye et al., 2006; Huppi et al., 1998; Miller et al., 2002; Neil et al., 1998; Schneider et al., 2004). Using tractography or region-of-interest approaches, these studies demonstrated, based on a linear model, significant age-related changes in diffusion indices, where fractional anisotropy (FA) increased and diffusivity values decreased, in most WM structures measured during the preterm and term periods as well as in the first few months of life. Nevertheless, a recent *in utero* DTI tractography study in normal fetuses between 23 and 38 gestational weeks depicted structure-specific non-linear curves of normalized FA and mean, axial and radial diffusivities (MD, AD and RD, respectively) as a function of age in different WM tracts (Zanin et al., 2011). Polynomial curve fitting with respect to age demonstrated three different phases, related by the authors to axonal organization, myelination gliosis, and myelination.

Magnetization transfer imaging (MTI) is another method used to assess brain development. It is sensitive to the concentration of semisolids in the tissue and therefore can be used for investigating white as well as gray matter maturation (Engelbrecht et al., 1998). A handful of studies have demonstrated positive linear evolution of magnetization transfer ratio (MTR) values with age in different selected WM and gray matter (GM) regions during early development (Engelbrecht et al., 1998; Nossin-Manor et al., 2012; van Buchem et al., 2001; Xydis et al., 2006a,b).

In a previous work we demonstrated the use of MTI and DTI to create group-wise average parametric maps characterizing tissue microstructure of the neonatal brain in very preterm infants (24–32 gestational weeks) scanned at preterm and term equivalent age (Nossin-Manor et al., 2013). Using a region-of-interest and voxel-based approach, we showed that these parametric maps present distinct contrasts whose interrelations varied across brain regions and between the preterm and term period, corresponding to various aspects of brain maturation such as tissue organization and myelination. MTR values showed a marked change in the pattern of regional variation at term equivalent age compared to the preterm period, such that the ordinal ranking of regions by signal contrast changed, corroborating myelination, for example, in the posterior limb of the internal capsule (PLIC). This was unlike DTI parameters where the regional ranking was similar at the two time points. Interpreting the data in terms of myelination and structural organization, we reported on the concordance with previous histological findings and demonstrated the value of multi-contrast MRI for tracking various aspects of brain maturation over the neonatal period.

In the present study we use MTI and DTI along with structural imaging, group-wise image registration, semiautomatic segmentation and voxel-based linear regression analysis for obtaining volumetric regression coefficient maps that describe population based developmental trajectories in the very preterm brain between 28 and 32 gestational weeks. Looking at the evolution of MTR and DTI indices with age, we follow spatiotemporal variations in cerebral maturation using *in vivo* data. Our goal was to determine distinct region-specific cerebral developmental trajectories over the whole brain and corroborate them with known cellular events occurring during the preterm period such as cell migration, the gradual regression of radial glial fibers, the development of axonal circuitry and the disappearance of the radial coherence, the gradual disappearance of the subplate and pre-/early myelination events.

Materials and methods

Subjects

The study included 18 preterm neonates, nine male, born between 27 and 31 gestational weeks (mean ± SD, 29.4 ± 1.2 weeks) and scanned within 2 weeks after birth (age range, 28–32 weeks; mean ± SD, 30.8 ± 1.4 weeks) without sedation. Neonates presented with normal findings on conventional MR images (T_1-, T_2-, T_2^*- and diffusion-weighted) ($n = 17$, including one with non-specific minor globi pallidi T_1 hyperintensity, probably due to total parenteral nutrition (TPN) administration with Manganese), and grade II intraventricular hemorrhage with no extension to the brain parenchyma or evidence of ventricular dilatation ($n = 1$). None had evidence of genetic, metabolic or viral infection disorders. MRIs were acquired between March 2008 and April 2010 as a part of a broader cohort of a prospective longitudinal study of 105 preterm neonates. Exclusion criteria for the present analyses included white matter and deep gray matter injuries, grade III intraventricular and grade IV intraperenchymal hemorrhages, and ventriculomegaly. Furthermore, only neonates who had a complete and successful (no susceptibility artifacts or severe motion) multi-contrast MRI session were included. All data sets were visually inspected; scans rejected for severe motion had rotation > 0.12 rad and displacements on the order of 3–5 mm (2D scans) but also included scans showing strong artifacts or signal loss (2D and 3D scans). DTI data was rated by two of the authors (RNM and DC) for severe, moderate and mild (rotational/translational) motion. Adequate data sets were chosen upon agreement between the raters. Out of 22 neonatal data sets passing these criteria, four data sets were excluded as MTR volumes were acquired after a scanner upgrade when the pulse type and angle of the MT pulse changed. Radiological assessments were completed by a neuroradiologist with >10 years of experience in neonatal imaging. The study was approved by the hospital's research ethics board, and informed, written consent was given by the infants' parents.

MR acquisition

All scans were completed on a 1.5 T GE Signa Excite HD scanner (GE, Milwaukee, WI) using an MR-compatible incubator and neonatal head coil (AIR, Inc., Cleveland, OH) according to a published imaging protocol (Nossin-Manor et al., 2013). To summarize the sequences analyzed here