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Probabilistic maps of the white matter tracts with known associated functions on the neonatal brain atlas: Application to evaluate longitudinal developmental trajectories in term-born and preterm-born infants

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ABSTRACT

Diffusion tensor imaging (DTI) has been widely used to investigate the development of the neonatal and infant brain, and deviations related to various diseases or medical conditions like preterm birth. In this study, we created a probabilistic map of fiber pathways with known associated functions, on a published neonatal multimodal atlas. The pathways-of-interest include the superficial white matter (SWM) fibers just beneath the specific cytoarchitectonically defined cortical areas, which were difficult to evaluate with existing DTI analysis methods. The Jülich cytoarchitectonic atlas was applied to define cortical areas related to specific brain functions, and the Dynamic Programming (DP) method was applied to delineate the white matter pathways traversing through the SWM. Probabilistic maps were created for pathways related to motor, somatosensory, auditory, visual, and limbic functions, as well as major white matter tracts, such as the corpus callosum, the inferior fronto-occipital fasciculus, and the middle cerebellar peduncle, by delineating these structures in eleven healthy term-born neonates. In order to characterize maturation-related changes in diffusivity measures of these pathways, the probabilistic maps were then applied to DTIs of 49 healthy infants who were longitudinally scanned at three time-points, approximately five weeks apart. First, we investigated the normal developmental pattern based on 19 term-born infants. Next, we analyzed 30 preterm-born infants to identify developmental patterns related to preterm birth. Last, we investigated the difference in diffusion measures between these groups to evaluate the effects of preterm birth on the development of these functional pathways. Term-born and preterm-born infants both demonstrated a time-dependent decrease in diffusivity, indicating postnatal maturation in these pathways, with laterality seen in the corticospinal tract and the optic radiation. The comparison between term- and preterm-born infants indicated higher diffusivity in the preterm-born infants than in the term-born infants in three of these pathways: the body of the corpus callosum; the left inferior longitudinal fasciculus; and the pathway connecting the left primary/secondary visual cortices and the motion-sensitive area in the occipitotemporal visual cortex (V5/MT+). Probabilistic maps provided an opportunity to investigate developmental changes of each white matter pathway. Whether alterations in white matter pathways can predict functional outcomes will be further investigated in a follow-up study.

Introduction

Diffusion tensor imaging (DTI) has been widely used to investigate the development of neonatal and infant brains and alterations related to various diseases or medical conditions (Huppi et al., 1998). Whole-brain DTI analysis based on tract-based spatial statistics (TBSS) (Smith et al., 2006), which is suitable for detecting alterations of white matter tracts with high fractional anisotropy (FA), has been applied to evaluate various conditions associated with prematurity at birth: chronic lung

Abbreviations: AAL, automated anatomical labeling; ABA, atlas-based analysis; DP, dynamic programming; DTI, diffusion tensor imaging; EPI, echo planar imaging; FA, fractional anisotropy; LDDMM, large deformation diffeomorphic metric mapping; MGB, medial geniculate body; RF, radio frequency; ROP, retinopathy of prematurity; SENSE, sensitivity encoding; SWM, superficial white matter; TBSS, tract-based spatial statistics; TOI, tracts-of-interest.

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disease (Ball et al., 2010); hypoxic–ischemic injury (Gao et al., 2012); hypercapnic ventilation (Ball et al., 2010); small-for-gestational-age infants (Lepomaki et al., 2013); and the neuro-protective effect of erythropoietin therapy for preterm infants (O'Gorman et al., 2015). The major strength of TBSS is the ability to identify highly localized "hot spots" for group differences, without an a priori hypothesis. Atlas-based analysis (ABA) is an alternative whole-brain analysis method, in which brain structures are parcellated into more than 100 anatomical structures that cover the entire brain, and parcel-by-parcel statistical analysis is performed (Oishi et al., 2012). ABA can evaluate the developmental status of individual anatomical units, including gray and white matter structures (Kersbergen et al., 2014; Loh et al., 2012; Oishi et al., 2013; Oishi et al., 2011c; Rose et al., 2014a), and allows the extraction of anatomical features from images that are combined with non-imaging clinical information (Rose et al., 2014b). The tracts-of-interest (TOI) method, in which white matter bundles are defined by tractography and tract-by-tract statistical analysis is performed, is well suited for the evaluation of major white matter bundles that are consistently observed in the human brain (Shi et al., 2014; Taylor et al., 2015). The fiber tracts mapped on images for the TOI are similar to a "roadmap" that visualizes connections between different areas, while parcellation maps from ABA are similar to an "area map" that defines the boundaries of each local region. The TBSS, ABA, and TOI methods are complementary to each other, and altogether, have contributed to the study of the early development of major white matter bundles. Namely, there is a general tendency toward a sharp increase in FA and a decrease in diffusivity measures during the first two years of life, but with variations depending on structures (Mukherjee et al., 2001; Saksena et al., 2008; Trivedi et al., 2009a; Yap et al., 2013; Zhang et al., 2007; Zhang et al., 2005). The limbic fibers are among the most developed structures at birth with the projection (e.g., corticospinal tract or spinothalamic tract) and the commissural (e.g., CC (corpus callosum)) fibers that develop from bottom-to-top and central-to-peripheral directions (Dubois et al., 2006; Gilmore et al., 2007; Huang et al., 2006; Huppi et al., 1998; Yap et al., 2013). The association fibers are the last to mature (Dubois et al., 2008; Huang et al., 2006; Zhang et al., 2007). This observation in DTI measures is congruent with patterns of myelination and axonal growth during early development (Kinney et al., 1988). The FA and diffusivity measures indicated a posterior-to-anterior direction of maturation within white matter regions (Oishi et al., 2011c; Rose et al., 2014a), although there is some controversy about the CC (Braga et al., 2015). Posterior portions of the CC and the projection fibers become detectable in deterministic tractography after their anterior counterparts (Huang et al., 2006). Among DTI measures, the FA increase is affected by tract organization (alignment, direction, and fiber-crossing), and the reduction in diffusion is sensitive to myelination, water content, and macromolecular concentration during early development (Gilmore et al., 2007; Mukherjee et al., 2002; Oishi et al., 2011c).

However, little is known about the development of the superficially located white matter fibers (SWM) (Oishi et al., 2011b; Oishi et al., 2008; Reveley et al., 2015). Investigation of the SWM of the neonatal brain is challenging because there is minimal myelination in neonatal and infant brains, which may lead to very low FA values. Since FA is too low, TBSS, or the conventional TOI methods that target high-FA white matter tracts, are unable to investigate these fibers. Moreover, delineating fibers passing through fiber-crossing areas such as the SWM is difficult with existing deterministic tractography, which relies on the first eigenvector of the tensor. ABA can be used to investigate the SWM (Oishi et al., 2008) although existing neonatal atlases (Brown et al., 2014; Kuklisova-Murgasova et al., 2011; Oishi et al., 2011c; Serag et al., 2012; Shi et al., 2014) do not include specialized parcellation maps for the investigation of the SWM. Since these SWM fibers connect between specific functional cortical regions, measuring the developmental trajectories of the SWM may provide early indicators that reflect developmental milestones, or predict functional outcomes.

In this study, we investigated white matter pathways known to be associated with various functions including the motor, somatosensory, visual, auditory, and limbic systems, which travel through the SWM areas, and other major white matter fiber tracts, based on our hypothesis that the developmental status of these pathways is related to corresponding functional developments. As an initial step, we created probabilistic maps of neonatal functional pathways on the published neonatal multimodal atlas (Oishi et al., 2011c) to quantify DTI-derived measures of these pathways. These functions include motor, somatosensory, auditory, visual, and limbic systems, the status of which is important as these are the developmental milestones of early life (http://www.nlm.nih.gov/medlineplus/infantandnewborndevelopment.html). The pathways inevitably include SWM fibers just beneath the specific cytoarchitectonically defined cortical areas, which have been difficult to evaluate with existing analysis methods. The two major challenges were: to define cytoarchitectonically defined cortical areas that are usually invisible on conventional MRI or DTI; and to delineate fibers that course through the SWM. We applied the Jülich cytoarchitectonic atlas (Eickhoff et al., 2005) to define cortical areas related to specific brain functions, and the Dynamic Programming (DP) method (Li et al., 2014; Ratnanather et al., 2013) to delineate the white matter pathways that course through the SWM. DP enables delineation of fibers within fiber-crossing areas using a probabilistic framework. Twenty-six white matter tracts that were categorized into one of the functional pathways (motor, somatosensory, auditory, visual, and limbic pathways), or major white matter bundles, such as the fronto-occipital fasciculus, the CC, and the middle cerebellar peduncle, were delineated on DTIs of 11 normal-term neonates, and normalized to the neonatal atlas. These tracts were binarized and then averaged to create probabilistic maps in the atlas space. To investigate maturation-related diffusion characteristics, the probabilistic maps were applied to DTIs of term- and preterm-born infants, who were longitudinally scanned at three time-points, at approximately five-week intervals, when the brain has the most rapid growth (Holland et al., 2014). We investigated the developmental patterns of term-born and preterm-born infants, and the effects of preterm birth on the developmental pattern.

Methods

Creation of probabilistic maps

Neonates

Eleven de-identified DTIs of term-born neonates (four boys and seven girls born at 38 to 41 postmenstrual weeks, and scanned within three days of life) were used to create the probabilistic atlases. The neonates were born at the Johns Hopkins Hospital. For the database creation, approval was obtained from the Johns Hopkins Medicine Institutional Review Board and the neonates' parents provided written, informed consent. These eleven DTIs were used only for the creation of the probabilistic maps, and not used for the application study described in 2.2.

MRI scans

Scans were performed without sedation on sleeping neonates. Images were acquired using a 3.0 T Philips scanner equipped with gradients of up to 8.0 G/cm per direction. The radio frequency (RF) was transmitted through a body coil and the receive coil was an eight-element sensitivity encoding (SENSE) coil, in which two of the coils were combined to be connected to a six-channel receiver. Single-shot echo planar imaging (EPI) with SENSE acquisition was used for DTI (Bammer et al., 2001; Jaermann et al., 2004; Pruessmann et al., 1999). The imaging matrix was 80×80 with a field-of-view of 150×150 mm, which gave a nominal 1.88 mm isotropic in-plane resolution. These were zero-filled to 256×256 mm. The slice orientation was axial with a 1.9 mm thickness parallel to the anterior–posterior commissure line. Forty to fifty slices covered the entire brain. Echo time was 71 ms and repetition time was