Cortical Folding and Connectivity in the developing brain

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Abstract
Understanding early human brain development is of great clinical importance, as many neurological and neurobehavioral disorders have their origin in early structural and functional cerebral organization and maturation. Cortical folding and establishment of underlying connectivity characterize early human brain development. Both conventional MRI and Diffusion tensor imaging (DTI), combined with advanced image analysis tools are powerful techniques to explore the structural basis of normal and abnormal brain development. With the development of 3D fiber tractography, the establishment and maturation of white matter connectivity can be followed with the potential to study correlations between abnormalities on DTI and ultimate neurologic/cognitive outcome.

Introduction:
The developing human brain presents several challenges for the application of DTI. Values for the water diffusion parameters differ markedly between pediatric brain and adult brain and vary with age. Yet in these challenges also lies opportunity, as changes in water mean diffusivity and diffusion anisotropy during development provide unique insight into the structural basis of brain maturation. In this course, we will discuss the cortical folding process and changes in the cortical phenotype and well as the application of DTI Tractography to study underlying white matter connectivity and post-injury plasticity.

Cortical Folding
Human brain growth takes largely place during the third trimester with whole brain volume more than doubling and cortical grey matter volume increasing fourfold (1) and an increase in subcortical grey matter or basal ganglia of 70% (2). This is also the time period in which cortical folding and gyrification takes place with an increase of brain surface and degree of sulcation index (3). So far, several hypotheses have been put forward on the mechanisms that underlie the folding process during development, but the potential influence of genetic, epigenetic and environmental factors is still poorly understood. According to post-mortem observations of foetal brains, the primary folds would form in a relatively stable spatio-temporal way during intra-uterine life depending on physical constraints and mechanical factors (4). An attractive theory suggests that the specific location and shape of sulci are determined by the global minimization over the brain of the visco-elastic tensions from white matter fibers connecting cortical areas (5, 6). This may explain why specific abnormalities in the sulcal pattern are observed in certain brain developmental disorders that are the result of subtle impairments in the neuronal migration and setting up of cortico-cortical connections (7, 8). However, reliable measurements on the normal cortical folding may only be obtained in vivo since post-mortem studies may be influenced by deformations of fixed brains and are intrinsically limited for longitudinal follow-
ups. Magnetic resonance imaging (MRI) has opened up the possibility to quantify this cortical development \textit{in vivo} in the human newborn brain (3) given its non-invasiveness, the provided contrast between cerebral tissues and the opportunity to analyze quantitatively the resulting images. The approach included a reconstruction of the interface between the developing cortex and white matter zone coherently in 3D using, which enabled a quantitative and \textit{in vivo} mapping of the individual sulci appearance during human brain development (Figure 1).

![Figure 1 Inner cortical surface reconstructions:](image)

Examples of the 3D interface between the developing cortex and white matter zone for newborns of different gestational age (in weeks, left numbers) and sulcation index (right numbers). The colors outline the surface curvature. The surfaces are not displayed with the same spatial scale.

In recent studies early alteration of cortex formation have been highlighted at birth according to intra-uterine environment, and related to infants’ neurological outcome at term equivalent age(9). Early differences were highlighted among newborns who experienced different intra-
uterine environment, with harmonious delay in twins and early impairment in newborns with intrauterine growth restriction. IUGR newborns showed a disruption of the developmental profile. The gyrification was not as delayed according to age as it should be in relationship with the delayed volumetric and surfacic growth, and the sulcation index was too high for equivalent surface in IUGR newborns compared with normal newborns. This progression in sulci and gyri formation despite the reduced cortical expansion suggests the importance of external factors like the tension from white matter fibers, measurable by DTI.

**DTI: Tractography**

Fiber tracking is a recent technique applied to the developing brain to study quantitative assessment of specific pathway maturation in white matter (10). Berman et al. (11) were able to show significant differences in the maturational changes in fractional anisotropy and transverse diffusion between the motor and the somatosensory pathway in premature infants between 30 and 40 weeks gestational age. This approach further allowed the measurement of diffusion changes across multiple levels of the functional tract and therefore the assessment of myelination progress over a given white matter fiber tract (11, 12). Gilmore et al., using a different tractography-based approach to measure mean diffusivity and fractional anisotropy changes within the corticospinal tract and the corpus callosum in the newborn, further showed a high intrarater reliability for the tract-based approach which was similar to manual techniques and improved detection of peripheral tracts compared to the manual technique (13).

Huang et al. (14) studied the appearance of most white matter fiber tracts in early development, comparing postmortem species from 19-20 weeks with in vivo term newborn’s and 5-6-year-old children’s DTI, and showed the early appearance of limbic fiber structures such as the cingulum and the fornix and, with the association fibers developing later, the absence of superior longitudinal fasciculus in the fetal brain around 19-20 weeks, only barely traceable at birth. The projection fibers developed earlier for the proximal segments of the posterior limb of the internal capsule, the cerebra peduncle, but later for the corona radiate, areas not visible in the fetal and neonatal brain. It is clear that absence of tract identification with DTI using current resolution and signal to noise level of images does not necessarily mean anatomical absence of the fiber tract system. Hermoye et al. further defined tract-specific maturation from term newborn to 4 years of age with most important changes occurring during the first 12 months (15). From 6 years to 17 years, FA increased only slowly and mean diffusivity decreased somewhat in most studied association and projection tracts (16).

In order to understand the underlying structural changes for the rapid development of motor and cognitive functions in the early months of postnatal life Dubois et al. (17) defined relative maturation phases of different white matter fiber tracts. This approach confirms prior ex vivo data on differential maturation in white matter tracts with corticospinal tracts appearing as the most mature bundle in the first 4 months of life and the anterior limb of the internal capsule and the cingulum as a limbic structure as the least mature bundles. Furthermore, this study allowed the differentiation of maturational stages within a functional system, for example with the fornix in the limbic system being in an advanced maturational phase compared to the cingulum, fornix being involved in associative learning, which is important in early functional development.

(Figure)
Tract-based spatial statistics analysis (TBSS) combined with probabilistic tractography is yet another method of defining changes in microstructure of the developing brain (18, 19). It starts to define a white matter tract skeleton thresholded at a given FA value. This technique found important changes in regions within the centrum semiovale, frontal white matter and the genu of the corpus callosum that had a significantly lower FA in preterm infants imaged at term-equivalent age compared to term-born controls (18) thus assessing alterations of brain development in ex preterm infants. Further changes in FA during brain development were mainly due to changes in axial diffusivity and more pronounced between early adolescence and adulthood than between late childhood and adolescence (19) Factors that might influence the changes in axial diffusivity at this age are increased neurotubules, neurofilaments and glial cells and increased fiber coherence. Using this technique, widespread age-related increases in FA were found through adolescence into young adulthood (13-21 years of age) with the most significant increase in the right body of the corpus callosum and the right superior region of the corona radiate and, in particular, in the frontal lobe association fibers (19, 20) This data confirms earlier neuronanatomical description of slow maturation of the corpus callosum into adolescence and is in concordance with recent data showing a U-shaped development curve of the corpus callosum with peak values between 30 and 40 years (21) and the prominent changes in volumetric and cortical density studies occurring in the frontal white matter during adolescence (22). These long-term changes fit with the assumption that learning and experience, which
continue throughout adult life, are accompanied by structural changes. Experience related changes in diffusion characteristics have been shown in practicing piano players (23) and confirm the experience based structural plasticity in the brain.

Reference List


