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Diffusion tensor imaging of brain development

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Summary 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. Diffusion tensor imaging (DTI), a recent magnetic resonance (MR) modality which assesses water diffusion in biological tissues at a microstructural level, has revealed a powerful technique to explore the structural basis of normal brain development. In fact, the tissue organization can be probed non-invasively, and the age-related changes of diffusion parameters (mean diffusivity, anisotropy) reveal crucial maturational processes, such as white matter myelination. Nevertheless, the developing human brain presents several challenges for DTI applications compared with the adult brain. DTI may further be used to detect brain injury well before conventional MRI, as water diffusion changes are an early indicator of cellular injury. This is particularly critical in infants in the context of administration of neuroprotective therapies. Changes in diffusion characteristics further provide early evidence of both focal and diffuse white matter injury in association with periventricular leukomalacia in the preterm infant. Finally, with the development of 3D fiber tractography, the maturation of white matter connectivity can be followed throughout infant development into adulthood with the potential to study correlations between abnormalities on DTI and ultimate neurologic/cognitive outcome.

Introduction

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 maturation. With conventional magnetic resonance imaging (MRI) we have been able to delineate macroscopically early developmental events such as myelination and gyral development. Diffusion tensor imaging (DTI) is a relatively new MR modality that assesses water diffusion in biological tissues at a microstructural level.[1]

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. As a result, much of the knowledge regarding DTI derived from studies of mature adult human brain is not directly applicable to developing brain. 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.

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DTI may further be used to evaluate brain injury.[2] It is well known from studies of animals[3] and adult humans[4] that DTI can serve as an early indicator of stroke, often demonstrating image abnormalities on water diffusion maps well before conventional MRI. Early detection of injury is particularly critical in the context of administration of neuroprotective therapies to infants. These therapies must be initiated quickly in order to interrupt the cascade of irreversible brain injury.[5] Water diffusion maps derived from DTI may provide the means for this early detection of injury. Changes in diffusion characteristics further provide early evidence of both focal and diffuse brain injury in association with periventricular leukomalacia (PVL), the most common form of white matter injury in the preterm infant.[6] Finally, with the development of 3D diffusion tensor fiber tractography, maturation of white matter and its consequences for white matter connectivity can be followed throughout infant development into adulthood, with the potential to study correlations between abnormalities on DTI and ultimate neurologic/cognitive outcome.[7]

In this review, we will discuss the changes in DTI parameters associated with normal brain maturation as well as their response to brain injury.

DTI methodology

It is worth noting that the precise DTI parameters to employ are open to question. Diffusion parameters describing the brain's microstructure include the three diffusion tensor eigenvalues ($\lambda 1$, $\lambda 2$, $\lambda 3$, which represent diffusion along the three tensor principal axes, Fig. 1), the mean diffusivity and a mathematical measure of anisotropy. These parameters are calculated in each voxel of the image.

There is a general consensus that the orientationally averaged mean diffusivity (D_{av}) is a useful parameter to derive from the diffusion tensor and serves as an indicator

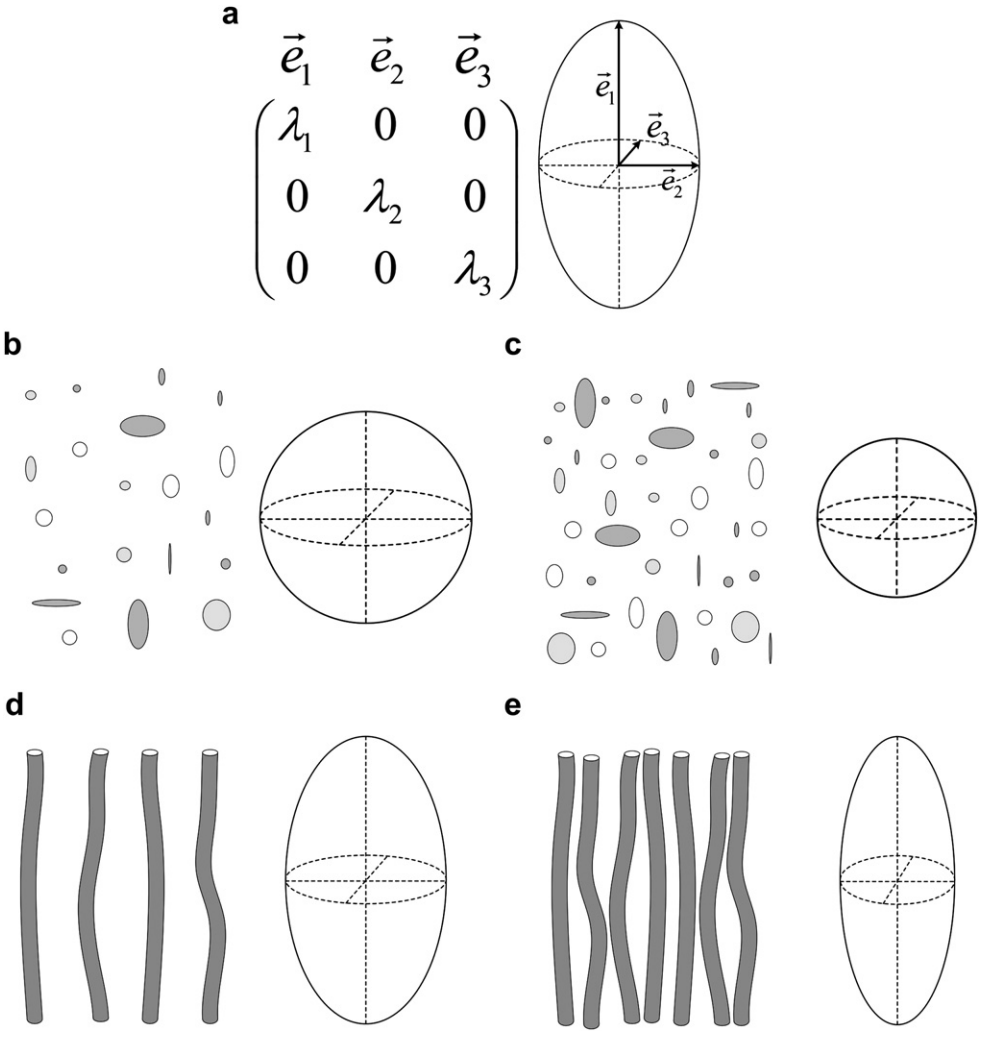

Figure 1 The diffusion tensor is generally characterized by a 3D ellipsoid (a), representing the diffusion isoprobability surface at the voxel level. The ellipsoid axes are oriented according to the tensor eigenvectors, and their length depends on the tensor eigenvalues. In an isotropic tissue (b) the ellipsoid is spherical, and the mean diffusivity depends on the tissue water content through the density of hindering structures (c). In white matter, fibers are oriented in bundles, diffusion is anisotropic (d), and the anisotropy increases with fiber density and decreasing membrane permeability (e).

of brain maturation and/or injury. D_{av} is calculated as one third of the trace of the diffusion tensor, $(\lambda1 + \lambda2 + \lambda3)/3$, and provides the overall magnitude of water diffusion independent of anisotropy.[8] In contrast, the description of water diffusion anisotropy used by different research groups varies (e.g. lattice anisotropy index, relative anisotropy, fractional anisotropy, color directional plots of anisotropy, 'vector maps' or 'whisker plots', gamma variate anisotropy images). These different representations of anisotropy are related to one another, their mathematical interconversions ranging from multiplication by a simple constant to complete recalculation using the underlying eigenvectors.[9] Further, the optimal means by which to evaluate water diffusion anisotropy remains an area of active investigation.[10] Relative anisotropy (RA) and fractional anisotropy (FA) are indicators of the degree of water diffusion anisotropy independent of the overall water diffusion coefficient. Both parameters are zero for isotropic diffusion (diffusion that is equal in all directions), and increase with anisotropy up to $\sqrt{2}$ and 1 for RA and FA, respectively. Notably, RA is linear over the total range of anisotropy values assuming cylindrical asymmetry,[9] whereas there is some indication that FA is more sensitive than RA to low anisotropies such as found in the immature brain.[10]

D_{av}, RA and FA are orientation-independent, meaning that they are not affected by the position of the subject in the MR scanner magnet relative to the orientation of the magnetic field gradients used to measure the diffusion values.

Vector maps, or RGB color-coded directionality maps,[11] indicate the orientation of the major eigenvector of the diffusion tensor, and are typically overlaid on structural images. They provide an indication of the direction in which water diffusion is highest, which typically is parallel to white matter fiber fascicles. On the contrary, the second and third eigenvectors describe diffusivity orthogonal to the axonal bundles.

Fiber tracking uses each voxel's primary eigenvector of the diffusion tensor to follow an axonal tract in 3D from voxel to voxel through the brain, thus allowing the delineation of specific cerebral white matter connectivity.

In order to perform DTI the *b* value at which to make the measurement has to be optimized, as it differs between the newborn and adult brain. In general, a *b* value corresponding to approximately $1.1/D_{av}$ provides the greatest contrast-to-noise ratio for such a measurement.[12] In adult humans, the high *b* value is typically on the order of 1000 mm^2/s. For the infant brain, which has higher values for D_{av}, *b* values on the order of 700–800 mm^2/s are used. Besides, higher SNR, with equivalent TE, is obtained as T2 is longer in the immature brain. Otherwise, similar MR pulse sequences and post-processing methods are used for both infant and adult human brain DTI. Nevertheless, the sensitivity of DTI images to motion during acquisition appears to be a crucial problem with unsedated newborns.[13]

DTI in normal brain development

D_{av} values are higher for pediatric than for adult brain. For example, D_{av} values for the white matter of the centrum semiovale in premature infants[14,15] approach 2.0×10^{-3} mm^2/s, while values for adult brain are typically 0.7×10^{-3} mm^2/s (for reference, D_{av} in free water at body temperature is approximately 3.0×10^{-3} mm^2/s). Thus, there is some restriction to water motion even for the highest D_{av} values measured in premature infants. During development, D_{av} values decrease with increasing age until they reach adult values.[16,17] D_{av} maps of pediatric brain show contrast between white and grey matter, with the D_{av} values for white matter being higher than those for grey matter (see Fig. 2). The precise cause of the decrease in D_{av} with increasing age is not known, although it has been shown to be influenced by both a decreasing water content and increasing complexity of white matter structures with increasing myelination.[15]

Brain water content decreases dramatically with increasing gestational age. As it does, structures that hinder water motion (e.g. cell and axonal membranes) become more densely packed, increasing restriction to motion, as if the brain becomes more viscous as its water content decreases (Fig. 1). That not all of the changes in D_{av} are due to reduction in overall water content is confirmed by measurements of the three eigenvalues $\lambda1$, $\lambda2$, $\lambda3$. During *white matter* development decreases in diffusion are observed principally in $\lambda2$, $\lambda3$ (and not in $\lambda1$), which reflect changes in water diffusion perpendicular to white matter fibers and may indicate changes due to premyelination (change of axonal width) and myelination.[16]

Differences in water content may also underlie the contrast present between white and grey matter in pediatric brain, though not in a simple fashion. In adult brain, the water content of white matter is substantially lower than that of grey matter (65% versus 85%),[18] yet the D_{av} values for the two regions are virtually identical.[19] This implies that white matter is less restrictive to water motion than grey matter at a given water content. This may be related to the fact that water motion parallel to axons is relatively unrestricted, especially in comparison to motion perpendicular to axons or in grey matter. In the premature brain, water content is similar in white and grey matter. The finding of higher D_{av} values in white matter than grey for premature brain despite their similar water content is also consistent with the idea that white matter is less restrictive to water motion than grey matter. In adult brain, this difference in restriction appears to be offset by the differing water contents of the two areas.

The changes in D_{av} are not necessarily simultaneous in all white matter regions. Partridge et al.[20] defined white matter maturation in commissural tracts such as the corpus callosum, in projection tracts such as the corticospinal tracts both inside the internal capsule as well as in the centrum semiovale, and in association tracts such as the cingulum or the inferior longitudinal fasciculus using a high-resolution DTI sequence. The lowest values of D_{av} were found in the projection fibers of the internal capsule and the cerebral peduncles with decreasing values from 30 weeks of gestational age to term age. The greatest decrease in D_{av} over the observed time period occurred in the lower centrum semiovale.[20]

Anisotropy values also differ between adult and pediatric brain.[21] For white matter areas, they are relatively low in infants and increase steadily with increasing age.[22] As with changes in values for D_{av}, changes in relative or

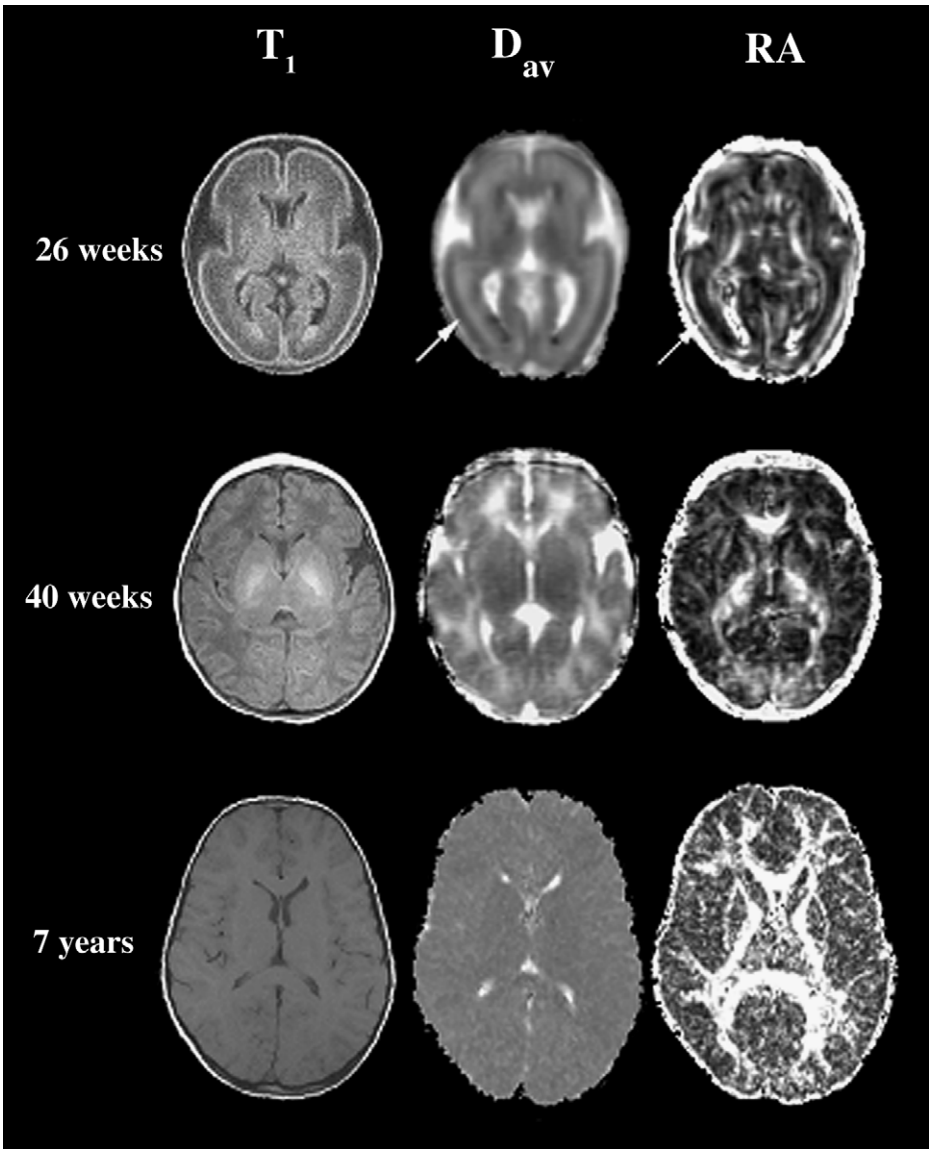

Figure 2 Axial images at the level of the basal ganglia from subjects of different ages. The top row is from a premature infant of 26 weeks' gestational age. The middle row is from a term infant of 40 weeks' gestational age. The bottom row is from a 7-year-old child. All three subjects were normal at the time of the study. The left column consists of T1-weighted images for anatomic reference. The center column consists of D_{av} parametric maps for which higher values of D_{av} appear brighter. The right column consists of relative anisotropy (RA) parametric maps for which higher values of RA appear brighter.[2] From Neil et al. (2002, *NMR Biomed* **15**:543—552) with permission.

fractional anisotropy take place more quickly early in development. While changes in D_{av} and anisotropy for white matter typically take place in tandem, with D_{av} values decreasing and anisotropy values increasing during maturation, it is important to bear in mind that the two parameters are theoretically independent of one another. Thus, a change in one is not always accompanied by the opposite change in the other (for example, the decrease of anisotropy of cerebral cortex that takes place between 26 and 32 weeks of gestational age is accompanied by a decrease in D_{av}).[2]

The increase in white matter anisotropy values during development appears to take place in two steps. The first increase takes place *before* the histologic appearance of myelin.[14,15] This increase has been attributed to changes in white matter structure which accompany the 'premyelinating state'.[23] This state is characterized by a number of histologic changes, including an increase in the number of microtubule-associated proteins in axons, a change in axon caliber, and a significant increase in the number of oligodendrocytes. It is also associated with changes in the axonal membrane, such as an increase in conduction velocity and changes in Na^+/K^+-ATPase activity. Interestingly, the commissural fibers in the splenium and the genu of corpus callosum express the highest fractional anisotropy values in the immature human brain.[20] These fibers are largely unmyelinated in the newborn period,[24] and their high anisotropy is in part due to a high degree of parallel

organization. The second, more sustained increase in anisotropy is associated with the histologic appearance of myelin and its maturation. The increase in anisotropy associated with premyelination is notable in that it takes place in the absence of changes in T1- or T2-weighted imaging as well as before the histologic appearance of myelin. Thus, it constitutes the earliest indication of impending myelination. The earliest signs of this second-stage change in anisotropy are observed in the projection fibers of the posterior limb of the internal capsule in the newborn period. This two-stage increase in white matter anisotropy takes place at different rates for different brain areas, as does brain maturation.[25] Regional anisotropy is clearly influenced by factors other than myelination alone, such as axon packing, relative membrane permeability to water, internal axonal structure, and tissue water content.

Besides, vector maps of white matter provide a visual indication of fiber bundles organization, and it is possible to produce an image of the overall orientation of white matter fascicles in a given area.

Another brain area in which anisotropy values differ between immature and mature brain is cerebral cortex. Anisotropy values of cortical grey matter in children beyond term and adult brain are generally consistent with zero, meaning that water diffusion in grey matter is isotropic at the spatial resolutions currently available. As has been shown in several human and animal studies, values for cortical grey matter in immature brain are transiently non-zero during development.[18,26–28] The tensor principal eigenvectors are then oriented radially to the cortical surface. A recent study on human fetal brain has shown that cortical anisotropy increases from 15 weeks' gestation to approximately 27 weeks' gestation, and then shows a gradual decline to 32 weeks' gestation.[29] The increase in anisotropy in this time period coincides with active neuronal migration along the radial glial scaffolding, whereas the decrease coincides with the phase of neocortical maturation with transformation of the radial glia into the more complex astrocytic neuropil. During the gestational ages for which anisotropy values are non-zero, cortical cytoarchitecture is therefore dominated by the radial glial fibers that are present across the cortical strata and by the radially oriented apical dendrites of pyramidal cells,[30] which is consistent with the vector orientations. With time, this architecture is disrupted by the addition of basal dendrites as well as thalamocortical afferents, which tend to be oriented orthogonal to the apical dendrites. Again these observations of microstructural brain development are not homogenous throughout the brain but show considerable regional differences, with cortical anisotropy decreasing first in precentral cortex, followed by occipital and frontal cortex[31] and even changing laterality throughout development.[29] Unlike the changes observed in immature white matter, the changes in fractional anisotropy observed in the cortex are mainly due to significant decrease in $\lambda 1$ with no changes in $\lambda 2$ and $\lambda 3$.[31] Thus, the relatively large decline in $\lambda 1$, oriented radially in cortex at 25–40 weeks' gestation, means that the maturational loss of cortical anisotropy is due to a reduction in the radial component of water diffusivity. Thus developmental changes in anisotropy of cerebral cortex reflect changes in its microstructure, such as the arborization of basal dendrites of cortical neurons, the innervation of the cortical plate by thalamocortical and cortico-cortical fibers, and transformation of radial glia into mature astrocytes — all processes which are an important basis of later functional connectivity.

The very immature brain is further characterized by a laminar organization with an immature cortical plate (as described above), a prominent subplate, an intermediate zone (corresponding to the later white matter) and the important area of germinal matrix, the origin of both neuronal and glial cell migration. This laminar organization can be visualized with vector maps both in the immature primate[28] and human brains.[18] Using an advanced voxel classification system, in which specific patterns of D_{av} and anisotropy are detected automatically, the immature human brain can be subdivided into cortical plate, subplate zone, and deep-to-subplate layers, including the intermediate zone, the subventricular zone, and the germinal matrix.[18] The germinal matrix itself was shown to express a gestational-dependent decrease in anisotropy from 15 weeks of gestation to about 32 weeks, when the germinal matrix starts to disappear.[29]

Fiber tracking is another recent technique applied to the developing brain to study quantitative assessment of specific pathway maturation in white matter (Fig. 3).[32,33] Berman et al.[34] 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 of gestational age. This approach further allowed measurement of diffusion changes across multiple levels of the functional tract.[34]

Alteration of white matter organization in preterm infants compared to full-term newborns have been shown using DTI.[14] As discussed below, this orientation may be disrupted due to injury. It is also worth noting that vector maps can be used to follow white matter tracts as they course through the brain.[35]

DTI and injury during brain development

Neonatal brain injury is most frequently related to hypoperfusion and/or hypoxemia followed by reperfusion as the infant is resuscitated, typically shortly after delivery or by chronic exposure to infection and inflammation. Hypotheses put forth to explain brain injury often take both mechanisms — hypoxia/ischemia and reperfusion and infection/inflammation — into account. Neuronal death appears to involve both necrosis and apoptosis.[36] Molecular mechanisms proposed to explain injury to both neurons and glia include accumulation of: cytosolic calcium, free radicals (including nitric oxide), cytotoxic amino acids, and cytokines.[37] Periventricular leukomalacia (PVL) is a unique pattern of neonatal brain injury involving primarily the cerebral white matter; it is most often found in preterm infants. Pathologic abnormalities are characteristically localized to the white matter dorsal and lateral to the external angles of the lateral ventricles and involve primarily the centrum semiovale.[38] This white matter region is thought to be especially vulnerable to injury in the preterm infant because of the nature of its blood supply and

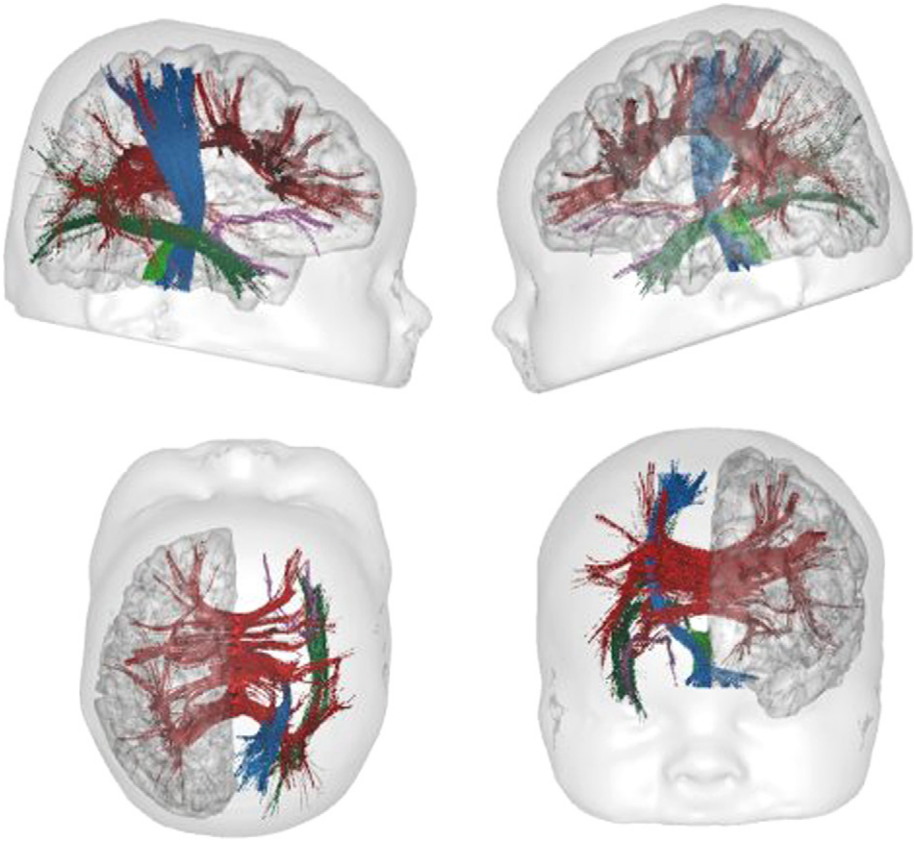

Figure 3 Major white matter fiber tracts in a 3-month-old infant.[33] The corpus callosum (red), the corticospinal (blue) and spinothalamic (light green) tracts, the inferior longitudinal (deep green) and uncinate (pink) fascicles are highlighted with tractography.

particular sensitivity to proinflammatory cytokines triggered by stimuli such as hypoxia/ischemia and infection.[39]

As indicated in the introduction, values for D_{av} decrease quickly after injury in most models studied, providing evidence of injury on maps of D_{av} before the injury is detectable on conventional imaging. The decrease in water diffusion associated with injury was initially described for animal[40,41] and adult human[4] stroke, and was subsequently confirmed for human infants.[42] Interpretation of apparent diffusion coefficient (ADC) values to detect acute brain injury in the developing brain needs to be adjusted for the regional differences in ADC values according to age (see Fig. 4).

There is still debate on the precise mechanism for the decrease in D_{av} associated with injury. Changes in D_{av} following injury are dynamic. D_{av} values are initially decreased, but subsequently increase so that they are greater than normal and remain so in the chronic phase of injury. During the transition between decreased and increased values there is a brief period during which values

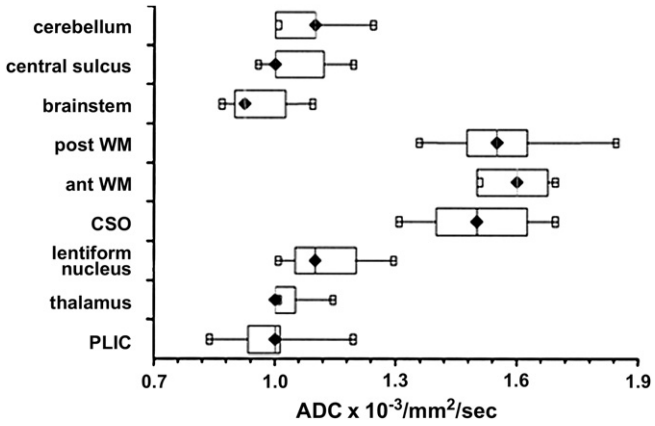

Figure 4 Regional ADC values in the newborn brain.[42]

are normal, a process referred to as 'pseudonormalization'. Pseudonormalization takes place roughly 2 days following stroke in a rat model[43] and at approximately 9 days following injury in adult human stroke.[44] Preliminary data indicate that the timing of pseudonormalization in human newborns more closely follows that of adult humans than rodents, taking place at roughly 7 days following the injury.[45] The time course of these changes is complex, however, and may vary somewhat with the nature of the injury (hypoxia/ischemia, inflammation, trauma), the relative vulnerability of different brain areas to injury, and other processes such as primary and secondary energy failure.[46] Given the dynamic nature of these changes, it has been suggested that a combination of conventional and DTI images and magnetic resonance spectroscopy (MRS) can be used to estimate the age of an injury to the central nervous system. During the first days following an injury, there are abnormalities on D_{av} maps, due to decreased water D_{av}, but not T2-weighted images. Subsequently, abnormalities are visible on both D_{av} maps and T2-weighted images. Roughly 1 week after the injury, the D_{av} map will become normal due to pseudonormalization, but the injury will be visible on T2-weighted images. With chronic injury, the lesion will be visible again on D_{av} maps, but now as an increase in water D_{av} rather than a decrease.[47]

The dynamic nature of the changes in D_{av} following injury makes it difficult to directly compare conventional MRI with DTI for detection of injury. Which method is most sensitive to injury — T2-weighted imaging, T1-weighted imaging, or D_{av} maps — varies with time after injury. Studies in which MRI is done at roughly 1 week after injury, the approximate time at which pseudonormalization takes place, tend to find that conventional imaging is as good as or better than DTI.[48] Studies in which the imaging is done somewhat earlier tend to find more utility for DTI.[49] Studies in which a series of images is obtained from the same infant over time[45] indicate that DTI is more useful during the first few days after injury, whereas conventional imaging — particularly T2-weighted or fluid-attenuated inversion-recovery (FLAIR) imaging — is more useful at later times. Overall, the primary difference between DTI and conventional imaging is the capability of DTI to often detect injury earlier. This may offer advantages in the future if neuroprotective agents become available and early detection of injury becomes important for deciding whether or not to administer them to a particular patient. It is worth noting, however, that DTI may not necessarily always demonstrate injury earlier than conventional MRI, and MRS might indicate metabolic alterations in otherwise normal imaging studies prior to 24 h after injury.[45,50–52]

Anisotropy of white matter also changes following injury. The changes appear to take place over several days to weeks. At the simplest level, anisotropy values are reduced dramatically in areas in which white matter is lost, such as porencephalic cysts.[53] Studies with pediatric and neonatal stroke also indicate that Wallerian degeneration is detectable as changes in anisotropy distant from the site of infarction.[54] Changes in anisotropy involving both anisotropy measurements and vector maps will likely prove especially relevant in premature infants, who tend to sustain injury to white matter. In the chronic stage of PVL, reductions in relative anisotropy may be present, and vector maps may show disruption of white matter tracts distant from the focal, cystic lesions detected by conventional imaging.[55] In this case, changes in anisotropy are detectable not only near the site of primary injury (the periventricular white matter), but also in the posterior limb of the internal capsule, indicating a disturbance of developing fibers which project through this area.[55] Thus, anisotropy and vector maps demonstrate injury that is not detectable by more conventional means. Further, changes in RA and fiber maps may provide insight into post-injury brain plasticity.[56,57] The clinical relevance of injury and related modification of white matter architecture detected in this fashion is not yet known, and long-term follow-up studies are currently under way.[58]

DTI and functional development during childhood

Finally, DTI parameters — particularly anisotropy — may be considered as structural markers of the networks functional organization and maturation, as proposed recently by correlation studies in children and adolescents. For instance, the development of working memory and reading capacities, between 8 and 18 years of age, is linked to the white matter anisotropy in regions of the left frontal and temporal lobes.[59] The maturation of these regions, as assessed by DTI, is correlated with the BOLD response amplitude, as measured by functional MRI.[58] Reading capacities in normal and dyslexic children[60,61] seem to depend on the organization and/or the myelination of temporo-parietal pathways, as described in adults.[62] Finally, diffusion parameters appear to be immature in children with functional developmental delay.[63] The application of DTI in the neonatal brain then provides an early assessment of its functional development, should it be normal or delayed.

Conclusions

Important changes in water ADC and diffusion anisotropy accompany brain maturation. These changes reflect changes in brain tissue microstructure. In the case of grey matter, this may reflect changes in the dendritic architecture of pyramidal cells and the presence or absence of radial glial fibers. In the case of white matter, it is due to the establishment of white matter fiber connection and changes related both to 'premyelination' and myelination itself. Thus DTI is a unique, non-invasive technique to study brain maturation which can be readily applied to human development. DTI-based fiber tracking allows study of the establishment of brain connectivity and plasticity during a time period of extreme importance for structural and functional integrity of the brain.

DTI also allows detection of changes in response to brain injury. Decreases in the water ADC serve as an early indicator of brain injury relevant for initiation of neuroprotective treatments. Regional, maturation-dependent differences in baseline diffusion coefficients need to be considered when interpreting injury-related diffusion abnormalities. Chronic changes in water anisotropy and the evaluation by DTI vector imaging are sensitive to injury-related impairment of subsequent white matter development and brain connectivity,

important early markers of later neurodevelopmental impairment. DTI in the newborn brain has allowed study of non-hemorrhagic brain injury early on, and has further opened up the possibility to study the structural correlate of functional impairment and plasticity in the developing brain.

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