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Using diffusion anisotropy to study cerebral cortical gray matter development

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ABSTRACT

Diffusion-weighted magnetic resonance imaging (diffusion MRI) is being used to characterize morphological development of cells within developing cerebral cortical gray matter. Abnormal morphology is a shared characteristic of cerebral cortical neurons for many neurodevelopmental disorders, and therefore diffusion MRI is potentially of high value for monitoring growth-related anatomical changes of relevance to brain function. Here, the theoretical framework for analyzing diffusion MRI data is summarized. An overview of quantitative methods for validating the interpretations of diffusion MRI data using light microscopy is then presented. These theoretical modeling and validation methods have been used to precisely characterize changes in water diffusion anisotropy with development in the context of several animal model systems. Further, in diffusion MRI studies of several preclinical models of neurodevelopmental disorders, the ability is demonstrated of diffusion MRI to detect abnormal morphological neural development. These animal model studies are reviewed along with recent initial efforts to translate the findings into an approach for studies of human subjects. This body of data indicates that diffusion MRI has the requisite sensitivity to detect abnormal cellular development in the context of several models of neurodevelopmental disorders, and therefore may provide a new strategy for detecting abnormalities in early stages of brain development in humans.

1. Introduction

This article is a contribution to the special issue of JMR recognizing the service of Joseph (“Joe”) Ackerman to the Journal. Joe Ackerman’s drive to understand the biophysical mechanisms that influence magnetic resonance signals measured in biological tissue profoundly shaped the body of data reviewed here. Joe designed many influential experiments that revealed how water diffusion, as encoded in diffusion-weighted magnetic resonance imaging (diffusion MRI) can be used to monitor brain physiology and anatomy on the cellular level. Many of these experiments were performed under his direction at the Biomedical MR Laboratory (BMRL) at Washington University. In the period from 2000 to 2005, I was fortunate to be a member of the BMRL and join the efforts of several researchers who were contributing to the efforts to develop a new way to non-invasively characterize anatomical development of cells within the cerebral cortex. This method utilized diffusion MRI in novel way. Rather than focusing on brain white matter structures, which at the time were known to induce anisotropy in water diffusion in ways that reflect their coherent organization as well as their pathophysiological characteristics in neurological disorders [1–3], the phenomenon being studied was water diffusion anisotropy within early developing cerebral cortical gray matter. Already by 1997, water diffusion anisotropy within the immature cerebral cortex had been reported in studies of cats [4] and pigs [5], and shortly thereafter Mori and co-workers characterized this phenomenon in the developing mouse brain [6]. Within the BMRL at this time, Jeff Neil was spearheading an effort to systematically study brain development within neonatal humans using diffusion MRI [7–9], with the objective to establish relationships between cellular-morphological development abnormalities revealed by this technique and the risk for subsequent cognitive and behavioral disorders in prematurely delivered human infants. Joe Ackerman integrated with this focused clinical objective a team of talented scientists in statistical physics, data analysis, biomechanics, cell biology neuroscience, neurophysiology, and small-animal MRI. Several of these individuals also share perspectives in this special issue of JMR.

This review summarizes contributions made in preclinical studies of the analysis of water diffusion anisotropy within developing cerebral cortical gray matter. Studies of animal model systems

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have facilitated the development of theoretical modeling strategies for analyzing the diffusion-attenuated MRI signal in gray matter as well as independent experimental methods for validating the interpretations of biophysical models. Further, they have enabled precise characterization of the normal trajectory of diffusion anisotropy changes with cortical maturation, and they have led to the generation of a series of animal model systems for assessing the value of diffusion MRI in identifying abnormal development. Joe Ackerman has facilitated this work through his mentorship individuals who subsequently positively affected the growth of this field and through direct contributions.

1.1. Diffusion within cerebral cortical gray matter: Dispersion in the orientation distribution of axons and dendrites

The cerebral cortex is the 1–5 mm-thick outer-most sheet of tissue in the mammalian brain. This is where synaptic connections reside that integrate sensory input, facilitate planning of responses, and instigate motor activities. A major focus for most diffusion MRI studies is the development, pathology, or anatomical organization of brain white matter. There are fundamental differences in the biological processes that influence water diffusion anisotropy in cerebral white matter compared to other brain structures. In white matter, axon fiber bundles that are comparable in size (length as well as cross-sectional area) to an MRI voxel restrict water diffusion perpendicular to the bundle more than in the direction parallel to the bundle. Degradation of the fiber bundle structure secondary to myelin or axonal injury, or disease, can result in reduced anisotropy in water diffusion [10,11]. Maturation of fiber bundles involves axonal organization and myelination, which are process associated with increases in water diffusion anisotropy [6,8,12]. Under each of these conditions, white matter exhibiting highly anisotropic water diffusion is associated with mature, healthy, often myelinated axons consisting primarily of parallel structures.

In addition to cerebral white matter, anisotropy in water diffusion can also be observed in gray matter. In particular, properties of water diffusion reflect cellular morphology in gray matter structures with laminar organization, such as the cerebral cortex and hippocampus (see [13] for a recent review). In the mature cerebral cortex, the majority of tissue volume consists of cylindrical cell processes such as axons and dendrites. Bourgeois and Rakic have estimated that approximately 60% of the cerebral cortex to be occupied by the "neuropil" at maturity [14]. Thus, on a microscopic cellular size scale, water diffusion is expected to be anisotropic. However, as a consequence of the broad distribution of cellular process orientations, water diffusion averaged over a volume of a standard diffusion MRI voxel in most gray matter stuctures exhibits very little directional dependence compared to most white matter structures. Water diffusion in the mature cerebral cortex is locally anisotropic but macroscopically nearly (but not completely [15,16]) isotropic. The immature cerebral cortex differs from the mature cortex in this regard. Immediately following migration of pyramidal neurons from ventricular and subventricular zones to the cortical plate, such as half way through gestation in humans or non-human primates, or the first days of life in mice and rats, most synaptic connections have not yet formed, and the morphology of neurons is simple (Fig. 1). Cellular processes within the cortical plate are nearly uniformly radially oriented, and correspondingly, water diffusion is as anisotropic as it is in mature white matter fiber bundles (e.g., see Fig. 4). In 2002, McKinstry and co-workers posited that water diffusion anisotropy changes associated with maturation reflect morphological changes in neurons and radial glia [9]. Healthy development is associated with reductions in water diffusion anisotropy, and as has been more explicitly refined since then, water diffusion anisotropy decreases with increasing dispersion in axonal and dendritic cellular process orientations (Fig. 1) [17]. It is important to precisely characterize the relationship between biological structures and cortical diffusion anisotropy because morphological development of neurons is reported to be abnormal in several neurodevelopmental disorders. If this abnormal morphology affects the trajectory of cortical FA changes with development, then the analysis of cortical FA could be of value for identifying individuals affected by neurodevelopmental disorders. This review summarizes work performed with several animal models of disease, in addition to studies of human subjects, that characterize the link between abnormal neural morphology and diffusion MRI studies focused on the developing cerebral cortex.

2. Biophysical modeling of water diffusion in the developing cerebral cortex

A common approach has been adopted for quantitative modeling of the influence of dispersion in the orientations of axon, dendrites, and other cylindrical cellular processes within a voxel [18–21]. This framework relies on three fundamental assumptions:

(1) Water molecules reside within one of two environments. The "cylindrical" environment consists of cellular processes such as axons and dendrites and is characterized by the volume fraction v. The "extra-cylindrical" environment consists of non-cylindrical structures such as cell bodies, and occupies the remaining 1-v volume fraction of the voxel.
(2) Water exchange between the two environments during the diffusion inter-pulse delay, Δ, is negligible.
(3) The Gaussian phase approximation is made within each environment.

The consequences of the first two assumptions are that the dependence of the signal intensity $S(b)$ on diffusion weighting b, relative to the reference intensity $S(0)$ can be written as the sum of two terms

$$S(b)/S(0) = vS_c(b) + (1 - v)S_e(b) \quad (1)$$

in which $S_c(b)$ and $S_e(b)$ correspond to the signal intensity components arising from the cylindrical and extracylindrical compartments, respectively, and b is the standard diffusion weighting term defined in diffusion measurements using pulsed-field gradient magnetic resonance techniques [22]. If water diffusion is assumed to be isotropic within the extracylindrical compartment, diffusion is characterized by the extracylindrical apparent diffusion coefficient (ADC_e) according to the expression

$$S_e(b) = \exp(-b \cdot ADC_e) \quad (2)$$

To account for anisotropic diffusion within the extracylindrical environment, the scalar-valued ADC_e can be replaced with a diffusion tensor D [23,24], as in [25].

Mathematical expressions for the cylindrical term $S_c(b)$ as a function of diffusion weighting oriented along an arbitrary diffusion sensitization direction, are first provided for the two limiting cases of extreme anisotropy of cellular process orientation, and perfectly isotropic orientation distribution of cellular processes. Under conditions of extreme anisotropy, all cylindrical cellular process are oriented parallel to each other, and α is the angle between this common orientation and the direction of the applied diffusion-sensitizing magnetic field gradients. Local diffusion anisotropy within the cylindrical structures is represented as a difference between the (larger) diffusion coefficient characterizing displacements parallel to the cellular process axis (D_{ax}) and the (smaller) diffusion coefficient characterizing displacements perpendicular to the cellular process axis, oriented radially in the local

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