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B-value dependence of DTI quantitation and sensitivity in detecting neural tissue changes

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ABSTRACT

Recently, remarkable success has been demonstrated in using MR diffusion tensor imaging (DTI) to characterize white matter. Water diffusion in complex biological tissue microstructure is not a free or Gaussian process but is hindered and restricted, thus contradicting the basic assumption in conventional DTI that diffusion weighted signal decays with b-value in a monoexponential manner. Nevertheless, DTI by far is still the fastest and most robust protocol in routine research and clinical settings. To assess the b-value dependence of DTI indices and evaluate their sensitivities in detecting neural tissues changes, in vivo DTI data acquired from rat brains at postnatal day 13, 21 and 120 with different b-values (0.5–2.5 ms/μm^2) and 30 gradient directions were analyzed. Results showed that the mean and directional diffusivities consistently decreased with b-value in both white and gray matters. The sensitivity of axial diffusivity ($\lambda_{//}$) in monitoring brain maturation generally decreased with b-value whereas that of radial diffusivity ($\lambda_{\perp}$) increased. FA generally varied less with b-value but in a manner dependent of the age and tissue type. Analysis also revealed that the FA sensitivity in detecting specific tissue changes was affected by b-value. These experimental findings confirmed the crucial effect of b-value on quantitative DTI in monitoring neural tissue alterations. They suggested that the choice of b-value in conventional DTI acquisition can be optimized for detecting neural tissue changes but shall depend on the specific tissue type and its changes or pathologies targeted, and caution must be taken in interpreting DTI indices.

Introduction

MR diffusion tensor imaging (DTI) has been shown to provide microstructural information in characterizing tissue microanatomy (Basser, 1995; Basser and Pierpaoli, 1996) that other non-invasive modalities cannot offer. Typical DTI indices, derived from the diffusion tensor as rotationally-invariant parameters, include fractional anisotropy (FA), mean (MD), axial ($\lambda_{//}$) and radial ($\lambda_{\perp}$) diffusivities. As water diffusion in nerve fibers is anisotropic due to myelination and other inherent axonal structures (Beaulieu, 2002), DTI has demonstrated remarkable success in probing the white matter (WM) integrity, and in describing the orientational neuroarchitecture and connectivity in the central nervous system (CNS). In recent years, DTI has been employed extensively to study the WM associated with both normal physiological and pathophysiological changes, including brain development and aging (Bockhorst et al., 2008; Qiu et al., 2008; Sullivan and Pfefferbaum, 2006; Verma et al., 2005), neurological and psychiatric disorders (Damoiseaux et al., 2008; Kolbe et al., 2009; Roosendaal et al., 2009; Rusch et al., 2007; Song et al., 2004; Sun et al., 2005), brain injuries and tumor (Chan et al., 2009a,b; Kidwell and Wintermark, 2008; Schonberg et al., 2006; Wang et al., 2008, 2009), and cognitive functions (Bucur et al., 2008; Qiu et al., 2008; Teipel et al., 2009).

The 2nd-order three-dimensional diffusion tensor (DT) model assumes that diffusion weighted (DW) signal has a monoexponential dependence on the diffusion-weighting factor (i.e., b-value). In other words, it assumes that water diffusion occurs in a free and unrestricted environment, yielding a Gaussian distribution of water diffusion displacement. However, the complex cellular or axonal microstructures in biological tissues hinder and restrict water molecule diffusion, and lead to restricted or non-Gaussian diffusion. DW signal from biological tissues is thus non-monoexponential with respect to b-value. In addition, because of the anisotropic nature of WM such as the corpus callosum, the extent of diffusion restriction is direction-dependent. Therefore, both directional diffusivities and FA can be b-value dependent, complicating the quantitative and comparative DTI studies.

Despite these fundamental limitations, conventional DTI is still the fastest, relatively robust and accessible protocol for investigation of water diffusion characteristics in neural tissues under routine clinical and research settings. Thus one key question is whether b-

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value in DTI can be optimized for characterizing the diffusion behaviors and/or their changes associated with specific cellular microstructure or pathology. A number of studies have been reported to optimize b-value for improving the detection of changes involved in brain development (Dudink et al., 2008; Jones et al., 2003), infarction (Meyer et al., 2000; Toyoda et al., 2007) and glioma (Alvarez-Linera et al., 2008; Seo et al., 2008). Several studies also investigated the effect of b-values on MD and FA derived in DTI (Jones and Basser, 2004; Melhem et al., 2000). However, the majority of these studies focused on MD and FA only. It is important to note that FA often cannot distinguish one pathologic condition from another because most pathologies, such as demyelination and axonal damage (Sun et al., 2006), would simply result in FA loss or reduction. Similarly, MD cannot provide the direction along which a specific pathology occurs. Given that the DTI directional analysis has been successfully demonstrated in previous studies for elucidating specific neural tissue pathologies in both humans and animal models (Ewing-Cobbs et al., 2008; Sizonenko et al., 2007; Song et al., 2002, 2003; Sun et al., 2006; Trip et al., 2006), it is imperative to investigate the b-value dependence of both FA and directional diffusivities, and its effect on DTI sensitivity in probing neural tissue alterations.

This study aimed to examine the quantitative effect of b-value on DTI indices, and to study the optimal b-value for detecting subtle changes in tissue microstructures. As brain development is accompanied by gradual and local morphological changes in both WM and gray matter (GM) (Bockhorst et al., 2008; Dubois et al., 2006; Huppi and Dubois, 2006), subtle changes in water diffusion characteristics are expected to occur during brain development. Therefore, the postnatal brain maturation in the well-controlled rat model was analyzed in the present study with in vivo DTI that employed various b-values.

Materials and methods

DWIs acquired from the postnatal developing rat brains in a recent study by our group (Cheung et al., 2009) were employed to derive DTI indices for various b-values. These DWIs were originally collected to evaluate the efficacy of diffusion kurtosis imaging. In brief, three groups of normal Sprague–Dawley (SD) rats were scanned. They were postnatal day 13 (P13), 31 (P31) and 120 (P120). Sample size was six for each age group. All experiments were conducted using a Bruker PharmaScan 7T scanner. DWIs were acquired with a respiration-gated 4-shot SE-EPI sequence with six different b-values (0.0, 0.5, 1.0, 1.5, 2.0, and 2.5 ms/μm^2) along 30 gradient encoding directions. For P13, a 23 mm birdcage quadrature RF coil was used for both transmission and receive. The imaging parameters were TR/TE = 3000/33.3 ms, $\delta/\Delta = 5/20$ ms, slice thickness = 0.7 mm, FOV = 25 mm, data matrix = 128 × 128 (zero-filled to 256 × 256) and NEX = 4 for P13 rats. For P31 and P120 rats, a birdcage transmit-only coil with a 72 mm inner diameter in combination with an actively decoupled receive-only quadrature surface coil was used. The imaging parameters were TR/TE = 3000/30.3 ms, $\delta/\Delta = 5/17$ ms, slice thickness = 1 mm, FOV = 30 mm × 30 mm, data matrix = 128 × 128 (zero-filled to 256 × 256) and NEX = 4. For each rat, DWIs were first co-registered before computing DT matrix using AIR5.2.5 (Woods et al., 1998a,b). All DTI index map computation was performed by a home-written MATLAB program. MD, FA, $\lambda_{//}$ and $\lambda_{\perp}$ maps were calculated from DWIs with two b-values, 0.0 versus 0.5, 1.0, 1.5, 2.0 or 2.5 ms/μm^2, respectively. These DTI index maps were also computed by fitting all DWIs with all six b-values to the monoexponential model $DW(b)/DW(0) = \exp(-bD)$.

Multi-slice region-of-interests (ROIs) were first defined in the FA maps as previously described (Cheung et al., 2009; Hui et al., 2008). They included four WM structures, including corpus callosum (CC), external capsule (EC), cerebral peduncle (CP) and anterior commissure (AC), and three GM structures, namely cortex (CT), hippocampus (HP) and caudate putamen (CU) as shown in Fig. 1. They were used to measure the average MD, FA, $\lambda_{//}$ and $\lambda_{\perp}$ values computed by DTI using various b-values (as well as all six b-values) in these tissue structures. These quantitative DTI indices were analyzed for their b-value dependence. To evaluate their sensitivity in detecting brain maturational changes, analysis of variance (ANOVA) was performed on these b-value specific measurements, followed by Tukey's test to examine their differences among three age groups. $+p<0.05$ and $\#p<0.01$ were considered as statistically significant. The sensitivities associated with different b-values were compared. For each specific b-value, the overall sensitivity was assessed by the number of statistical

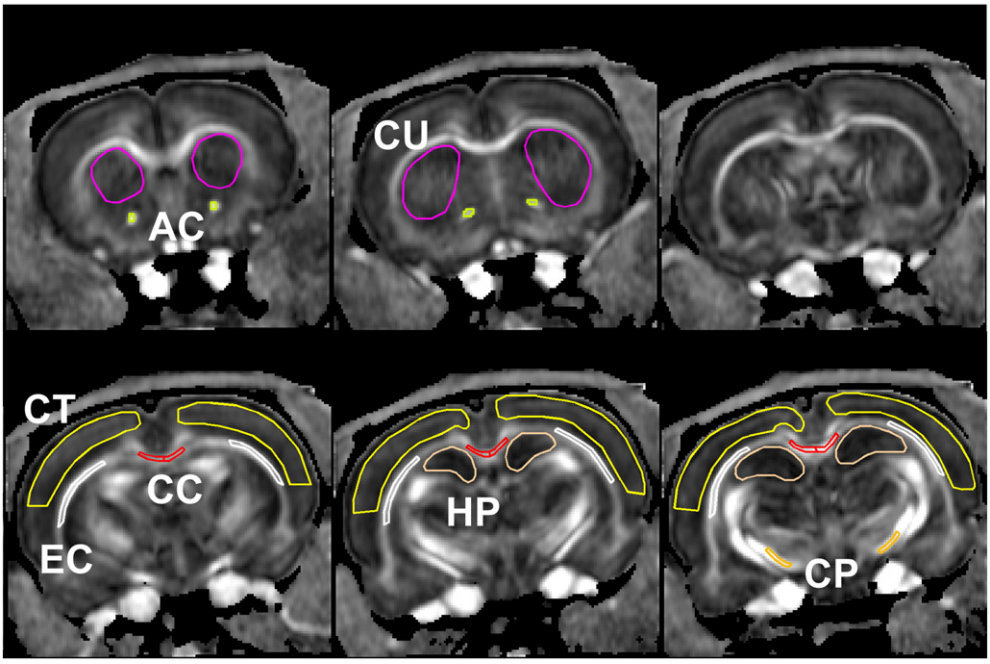

Fig. 1. Typical ROI definitions overlaid on the fractional anisotropy (FA) maps in a postnatal day 120 (P120) rat brain. ROIs were used to measure the DTI indices associated with various b-values used by DTI. Four WM structures, corpus callosum (CC), external capsule (EC), cerebral peduncle (CP), and anterior commissure (AC), and three GM structures, cerebral cortex (CT), hippocampus (HP), and caudate putamen (CU), were identified in the FA maps.