NeuroImage 57 (2011) 1087–1102

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Non-Gaussian diffusion in human brain tissue at high *b*-factors as examined by a combined diffusion kurtosis and biexponential diffusion tensor analysis

Farida Grinberg [a,*], Ezequiel Farrher [a], Joachim Kaffanke [a], Ana-Maria Oros-Peusquens [a], N. Jon Shah [a,b]

[a] Institute of Neuroscience and Medicine-4, Forschungszentrum Juelich GmbH, 52425 Juelich, Germany
[b] Department of Neurology, Faculty of Medicine, RWTH Aachen University, JARA, 52074 Aachen, Germany

ARTICLE INFO

Article history:
Received 4 March 2011
Revised 20 April 2011
Accepted 25 April 2011
Available online 6 May 2011

Keywords:
Diffusion tensor imaging
Diffusion kurtosis imaging
Biexponential tensor analysis
Human brain tissue
High *b*-factors
White matter mapping

ABSTRACT

Diffusion tensor imaging (DTI) permits non-invasive probing of tissue microstructure and provides invaluable information in brain diagnostics. Our aim was to examine approaches capable of capturing more detailed information on the propagation mechanisms and underlying tissue microstructure in comparison to the conventional methods. In this work, we report a detailed in vivo diffusion study of the human brain in an extended range of the *b*-factors (up to 7000 s mm^{-2}) performed on a group of 14 healthy volunteers at 3 T. Combined diffusion kurtosis imaging (DKI) and biexponential diffusion tensor analysis (BEDTA) were applied to quantify the attenuation curves. New quantitative indices are suggested as map parameters and are shown to improve the underlying structure contrast in comparison to conventional DTI. In particular, fractional anisotropy maps related to the slow diffusion tensor are shown to attain significantly higher values and to substantially improve white matter mapping. This is demonstrated for the specified regions of the frontal and occipital lobes and for the anterior cingulate. The findings of this work are substantiated by the statistical analysis of the whole slice histograms averaged over 14 subjects. Colour-coded directional maps related to the fast and slow diffusion tensors in human brain tissue are constructed for the first time and these demonstrate a high degree of axial co-alignment of the two tensors in the white matter regions. It is concluded that a combined DKI and BEDTA offers a promising framework for monitoring tissue alteration during development and degeneration or as a consequence of the neurological disease.

Introduction

Attenuation of the water nuclear magnetic resonance (NMR) signal by molecular diffusion in tissue provides valuable information regarding its microstructure and physiological condition. In particular, diffusion-weighted imaging (DWI) gave rise to outstanding opportunities in brain diagnostics and has become an indispensable tool in clinical practice. Unique applications refer to the diagnostics of acute stroke, tumours and various neurological disorders (Johansen-Berg and Behrens, 2009; Beaulieu, 2002; Le Bihan, 2007). A remarkable success is also associated with diffusion tensor imaging (DTI) utilising anisotropic water diffusion in white matter (WM) in order to access neuronal fibre pathways and connectivity (Basser and Jones, 2002; Le Bihan et al., 2001; Skudlarski et al., 2008). DTI was reported to be important in the assessment of various neurodegenerative diseases such as multiple sclerosis, epilepsy, or Alzheimer's disease (Assaf, 2008; Ciccarelli et al., 2008) and other cognitive disorders (schizophrenia, dementia) (Shin et al., 2006; Mayzel-Oreg et al., 2007). More recently, DTI studies were applied to characterization of white-matter structural changes accompanying brain maturation (Mukherjee and McKinstry, 2006; Paus et al., 2001) and normal ageing (Moseley, 2002; Michielse et al., 2010; Barrick et al., 2010). Many advanced techniques have been recently suggested for the reconstruction of the diffusion orientation distribution function with an enhanced angular resolution (Tuch, et al., 2002; Tuch, 2004; Tournier et al., 2004; Ozarslan, et al., 2006; Descoteaux, et al., 2007). DTI also offers promising perspectives in accessing brain function in combination with functional studies (Le Bihan, et al., 2006).

Neuronal tissue is highly heterogeneous on various length scales. Establishing a proper picture of the relationship between dynamics and structure requires differentiation between the various contributions to the average NMR response and is thus a very difficult task. The conventional DTI approach suffers from intrinsic limitations as it is based on the assumption of Gaussian free diffusion characteristic of non-confined isotropic liquids. Usually, DWI/DTI studies are performed for low diffusion weightings (*b*-values) using the monoexponential approximation. However, a clear departure from a monoexponential behaviour in the range of higher diffusion weightings has been reported (Mulkern et al., 2009; Cohen and Assaf, 2002; Clark and Le Bihan, 2000). The underlying mechanisms of these deviations are far from being well understood and remain controversially discussed in the literature. Potentially, the propagation of water molecules in the brain is affected

* Corresponding author. Fax: +49 2461 61 2820.
E-mail address: f.grinberg@fz-juelich.de (F. Grinberg).

1053-8119/$ – see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.neuroimage.2011.04.050

by multiple factors such as compartmentalization, restrictions and anisotropy imposed by the cellular microstructure (Johansen-Berg and Behrens, 2009). Interfacial interactions with the cell membranes ("bound water") and membrane permeability may further complicate the measured response (Beaulieu, 2002). In addition, the orientational ordering of axonal fibres on extended length scales gives rise to anisotropic diffusion which appears faster in the direction parallel to fibres than perpendicular to them.

More recently, increasing efforts (Le Bihan, 2007; Assaf and Basser, 2005; Jespersen et al., 2007; Posnansky and Shah, 2008; Descoteaux et al., 2009; Minati et al., 2007) have been devoted to the development of new models and empirical approaches exploiting the observed non-Gaussian diffusion patterns. Several methods of data analysis have been suggested, in particular, biexponential fitting (Clark et al., 2002; Maier et al., 2004; Maier and Mulkern, 2008; Kiselev and Il'yasov, 2007; Mulkern, et al., 2001; Mulkern et al., 2009), diffusion kurtosis imaging (DKI) (Jensen et al., 2005; Hui et al., 2008), stretched exponential function (Bennett et al., 2003), and the statistical model by Yablonskiy et al. (2003). Generally, the advantage of these methods is that they allow one to enhance the information obtained from DWI/DTI and they form the basis for the development of new tools in clinical diagnostics.

One of the approaches that has gained substantial attention from researchers was developed on the basis of simplified geometrical models (Sen and Basser, 2005) that are already well established in the studies of confined diffusion in porous media. It is based on the concept of compartmentalization of water molecules within the extracellular (ECS) and intracellular (ICS) spaces. In the ICS, diffusion would be more restricted giving rise to the slow diffusion component. However, a serious drawback of this model is that the relative volumes of the ICS and ECS known from histology appear in very different, nearly inverted, proportions to the experimentally measured fractions of the fast and slow diffusion components. Attempts have been made to overcome this discrepancy by consideration of relaxation effects and finite membrane permeability (i.e. exchange effects in terms of the Kärger two-site model (Kärger et al., 1988)). An alternative interpretation (Le Bihan, 2007) suggests an existence of two differently structured water pools in intermediate or slow exchange. Thus far, none of the proposed models has gained general acceptance. The field is still very poorly investigated and more statistical work remains to be done for a better understanding of the non-Gaussian nature of diffusion in brain parenchyma.

The aim of this work was to examine the potential benefits and drawbacks of performing in vivo diffusion magnetic resonance imaging (MRI) over an extended range of b-values and to obtain more detailed information on diffusion mechanisms and the underlying microstructure of brain tissue. Deviations of the diffusion attenuation curves from patterns of Gaussian diffusion are analysed in the framework of the combined DKI and biexponential diffusion tensor analysis (BEDTA). Maps of the new quantitative indices are reconstructed and discussed.

Theory and background

In the simplest case of normal isotropic diffusion, the normalised signal intensity, S, is given by Stejskal and Tanner(1965):

$$S(b) = \exp(-bD), \tag{1}$$

where D is molecular diffusivity, and b is a factor depending on the strength, g, and the duration, δ, of the magnetic field gradient pulses, and on their separation intervals, Δ. In the simplest Hahn-echo pulse sequence, 90°–180°, the factor b is given by Stejskal and Tanner (1965):

$$b = (\gamma\delta g)^2 t, \tag{2}$$

where g is the nuclear gyromagnetic ratio and $t = \Delta - \frac{1}{3}\delta$ is the observation time. By means of the Einstein relation, $\langle x^2\rangle = 2Dt$, the measured values of the diffusivity provide direct access to the molecular mean square displacements, $\langle x^2\rangle$, in the direction of the applied gradient during the observation time. Typically, the monitored displacements are in the range of a few micrometres, well below the voxel size. This, generally, makes diffusion experiments sensitive to details of the microstructure on a subvoxel level.

In heterogeneous and/or anisotropic environments, molecular propagation is affected by the presence of barriers and thus deviations from Gaussian behaviour, Eq. (1), occur. In such media, the slopes of the curves $S(b)$ are determined not only by intrinsic molecular diffusivities but also by the overall effect of various restrictions and constraints. Moreover, the evaluated values of D become dependent on experimental parameters such as the observation time or diffusion-encoding direction. Granting due recognition to the above, in brain MRI the measured slope of $S(b)$ is referred to as the Apparent Diffusion Coefficient (ADC). It is worth noting that, depending on measurement conditions, the ADC may be either related to, or be completely unrelated to the intrinsic diffusivity. The latter, for instance, occurs for diffusion in the closed cavities (Topgaard and Söderman, 2003).

Anisotropic ordering of axons on length scales exceeding one voxel size is an essential feature of the white matter microstructure. This gives rise to anisotropic diffusion of water molecules during the typical observation times. Diffusion appears faster in the direction parallel to the axonal long axis than in the perpendicular direction, and thus cannot be adequately accounted for with a single scalar parameter. The most widely used approach to deal with diffusion anisotropy in brain tissue is based on the tensor formalism. It implies that the response signal depends on the direction of the diffusion encoding gradients according to Basser et al.(1994) and Mattiello et al.(1994)

$$S(\mathbf{b}) = \exp\left(-\sum_{i=1}^{3}\sum_{j=1}^{3} b_{ij}D_{ij}\right), \tag{3}$$

where b_{ij} and D_{ij} are the elements of the symmetric b-matrix, $\mathbf{b}$, and of the apparent diffusion tensor, $\mathbf{D}$, respectively. Denoting the eigenvalues of the diffusion tensor as λ_1, λ_2, and λ_3, the mean apparent diffusivity, MD, and fractional anisotropy, FA, are determined by Basser and Jones(2002) as:

$$MD = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3}, \tag{4}$$

$$FA = \sqrt{\frac{3}{2}}\sqrt{\frac{(\lambda_1 - MD)^2 + (\lambda_2 - MD)^2 + (\lambda_3 - MD)^2}{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}. \tag{5}$$

In systems with cylindrical symmetry, the axial (λ^{axial}) and radial (λ^{radial}) eigenvalues are derived according to, $\lambda^{axial} = \lambda_1$ and $\lambda^{radial} = (\lambda_2 + \lambda_3)/2$ assuming that λ_1 is the highest eigenvalue.

Deviations of the signal attenuation from Eq. (1) due to the abovementioned heterogeneity first become considerable in the range of the b-factors exceeding the values of approximately 1000 s mm^{-2} commonly exploited in the conventional DTI. Amongst various approaches suggested for treating the data more adequately, two models are relevant for this study. These are the diffusion kurtosis imaging and the biexponential models which are briefly described below.

The simplest extension of DTI is based on evaluation of the model-free parameter known as excess kurtosis $K \equiv (\mu_4/\mu_2^2) - 3$, where μ_4 and μ_2 are the fourth and the second central moments of the probability distribution function, respectively. With respect to the diffusion propagator, excess kurtosis provides a dimensionless quantitative measure of the deviation