NeuroImage 120 (2015) 371–381

Contents lists available at ScienceDirect

NeuroImage

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

Double-pulsed diffusional kurtosis imaging for the in vivo assessment of human brain microstructure

Edward S. Hui [a,*], Jens H. Jensen [b,c]

[a] Department of Diagnostic Radiology, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Pokfulam, Hong Kong, China
[b] Department of Radiology and Radiological Science, Medical University of South Carolina, Charleston, SC, USA
[c] Center for Biomedical Imaging, Medical University of South Carolina, Charleston, SC, USA

ARTICLE INFO

Article history:
Received 19 January 2015
Accepted 5 July 2015
Available online 11 July 2015

Keywords:
Double-pulsed-field-gradient
Multiple-wave-vector
Microscopic anisotropy
Non-Gaussian diffusion
Kurtosis
Human

ABSTRACT

We have recently extended conventional single-pulsed-field-gradient (s-PFG) diffusional kurtosis imaging (DKI) to double-pulsed-field-gradient (d-PFG) diffusion MRI sequences, with a method known as double-pulsed DKI (DP-DKI). By virtue of a six-dimensional (6D) formulation for q-space, many of the results and insights of s-PFG DKI are generalized to those of DP-DKI. Owing to the fact that DP-DKI isolates the second order contributions to the d-PFG signal (i.e. second order in b-value), the 6D diffusional kurtosis encodes information beyond what is available from s-PFG sequences. Previously, we have demonstrated DP-DKI for in vivo mouse brain at 7 T, and it is the objective of this study to demonstrate the feasibility of DP-DKI at 3 T for the in vivo assessment of human brain microstructure. In addition, an example is given of how to utilize the additional information obtained from DP-DKI for the purpose of biophysical modeling. The relationship between a specific microscopic anisotropy metric estimated from DP-DKI and other recently proposed measures is also discussed.

Introduction

Diffusion tensor imaging (DTI) has become an invaluable tool for the in vivo assessment of neuroarchitecture. Of all DTI metrics, fractional anisotropy (FA) has been the most widely used biomarker for the characterization of white matter (WM) change in various neurological disorders. A premise of the FA is that it reflects the macroscopic anisotropy of water diffusion in WM that arises as a result of the coherent alignment of axonal fiber bundles. An alteration in fiber alignment or integrity, as in disease progression, can thus modulate the FA. However, because less than 10% of axonal fiber bundles are highly coherent, assessment of WM architecture using FA becomes ambiguous in a majority of WM voxels (De Santis et al., 2014). The classic case in point is the lower FA observed in regions with complex WM architecture, such as crossing or fanning fibers (Alexander et al., 2001). Moreover, FA is of limited utility in gray matter (GM), as GM has a low macroscopic anisotropy. This is in spite of GM having substantial microscopic diffusion anisotropy arising from water restricted by neurites (i.e., axons and dendrites) (Shemesh et al., 2010b). Improved means for quantifying the diffusion anisotropy of brain tissue with complex fiber geometries may potentially provide more sensitive and specific biomarkers of microstructural changes due to pathophysiological processes.

Mitra (1995) considered the application of pulsed-field-gradient (PFG) NMR with multiple wave vector diffusion encodings to the quantification of the diffusion dynamics for spins within porous media. The extension of this method to MRI is known variously as multiple-PFG, multiple-wave-vector, or multiple-pulsed diffusion MRI. The case with two diffusion-encoding wave vectors (i.e., double-pulsed diffusion MRI) (Shemesh et al., 2010b) is the simplest and most commonly utilized variant. Double-pulsed diffusion MRI has been applied by several groups as a means of assessing diffusion anisotropy (Callaghan and Komlosh, 2002; Jensen et al., 2014; Jespersen et al., 2013; Komlosh et al., 2007, 2008; Lasič et al., 2014; Lawrenz and Finsterbusch, 2011, 2013, 2014; Lawrenz et al., 2010; Ozarslan and Basser, 2008; Ozarslan, 2009; Shemesh and Cohen, 2011a; Shemesh et al., 2012a,2012b; Szczepankiewicz et al., 2014).

In a seminal paper by Jespersen (2012), it is shown that the information obtained with double-pulsed diffusion MRI and with conventional s-PFG experiments are equivalent at low diffusion weightings, although for higher diffusion weightings new information is accessible with d-PFG sequences. This follows from the fact that the standard diffusion tensor, as obtained with DTI, is sufficient for fully characterizing the diffusion MRI signal to leading order in the diffusion weighting for arbitrary pulse sequences (Jensen, 2014). In this low diffusion-weighting limit, the Gaussian approximation of DTI is all that is needed, since non-Gaussian diffusion effects are small. Thus for double-pulsed diffusion MRI to yield truly novel information, beyond what is provided by s-PFG methods, higher diffusion weightings must be applied so that non-Gaussian diffusion effects become substantial.

* Corresponding author at: Department of Diagnostic Radiology, Li Ka Shing Faculty of Medicine, The University of Hong Kong, LG3, Jockey Club Building for Interdisciplinary Research, 5 Sassoon Road, Pokfulam, Hong Kong, China.
E-mail address: edward.s.hui@gmail.com (E.S. Hui).

http://dx.doi.org/10.1016/j.neuroimage.2015.07.013
1053-8119/

In order to more conveniently quantify the leading non-Gaussian diffusion effects for double-pulsed diffusion MRI, we have recently introduced DP-DKI, which employs d-PFG sequences (Jensen et al., 2014). As a part of the DP-DKI formalism, the two three-dimensional (3D) diffusion wave vectors are interpreted as a single 6D wave vector. In this way, many of the concepts and formulae from conventional DKI may be generalized to DP-DKI in a straightforward manner. In particular, DP-DKI is able to compactly quantify all contributions to the d-PFG signal magnitude up to second order in the b-value. These second order contributions comprise the novel information that is, in practice, most easily measurable with double-pulsed diffusion MRI.

This novel information is closely linked to the notion of microscopic diffusion anisotropy. Most prior studies have conceived of microscopic anisotropy as encompassing macroscopic anisotropy, so that any medium with a nonzero FA would be regarded as possessing both macroscopic and microscopic anisotropy (Lasič et al., 2014; Shemesh et al., 2010b). We shall refer to this as "type I" microscopic anisotropy. Alternatively, one can define "type II" microscopic anisotropy as being diffusion anisotropy that can only be detected with multiple-PFG sequences. In this way, a medium (e.g., a single domain liquid crystal) could be macroscopically anisotropic without necessarily having type II microscopic anisotropy. While these two conceptions of microscopic anisotropy are closely related, type II microscopic anisotropy arises naturally out of the DP-DKI approach. For systems without macroscopic anisotropy, type I and type II microscopic anisotropy are equivalent and may both be nonzero. For example, water confined to an ensemble of many randomly oriented cylindrical pores is macroscopically isotropic (Shemesh et al., 2010a), even though the diffusion within each pore is highly anisotropic. This is called microscopic anisotropy, since measures that only quantify the anisotropy of the full ensemble are insensitive to this property.

Several related metrics have been proposed for quantifying type I microscopic anisotropy with double-pulsed diffusion MRI data. Lawrenz et al. (2010) derived a rotationally invariant metric of microscopic anisotropy for porous media, known as I_{MA}, from the Taylor series of the d-PFG signal in the long diffusion time limit. Shemesh et al. (2012a) also proposed a metric of microscopic anisotropy, known as apparent eccentricity index, which is derived from the dependence of d-PFG signal on the angle θ between the diffusion wave vector for the first and second blocks of PFG. Subsequently, Jespersen et al. (2013, 2014) introduced an apparent compartmental eccentricity that may be applied for all diffusion times and is proportional to I_{MA}, in the long diffusion time limit. They also defined a fractional eccentricity (FE) that recasts the same information in manner more analogous to the FA, so that the FE equals the FA whenever the type II microscopic anisotropy vanishes. With magic-angle-spinning diffusion MRI, one can also measure a "microscopic fractional anisotropy" (μFA) (Lasič et al., 2014; Szczepankiewicz et al., 2014). It is argued by Jespersen and coworkers that FE = μFA, although the exact equality depends on corrections included in an erratum (Jespersen et al., 2014).

In our previous work (Jensen et al., 2014), we have defined a general rotational invariant for DP-DKI, $\widetilde{\overline{W}}$, that is equal to the mean of the 6D diffusional kurtosis tensor averaged over all possible 6D directions. In addition, we have shown that, for multiple Gaussian compartment (MGC) models, $\widetilde{\overline{W}}$ provides information closely related to type II microscopic anisotropy. In this paper, we consider the relationship of $\widetilde{\overline{W}}$ to some of the indices of microscopic anisotropy discussed above.

We have previously described the DP-DKI formalism in detail and given preliminary results for mouse brain. Here our primary aim is to demonstrate the feasibility of the method for in vivo human imaging. Beyond this, we also expand upon the physical meaning of the diffusion metric $\widetilde{\overline{W}}$ and give an example of its application to tissue modeling of gray matter.

Methods

Theory

In this section, we will briefly describe the theory underlying DP-DKI; please refer to (Jensen et al., 2014) for a more detailed description thereof.

An example d-PFG MRI sequence consists of two blocks of diffusion gradients, one between the 90° excitation and 180° refocusing pulses, and the other after the 180° refocusing pulse (see Fig. 1). The pulse duration δ and diffusion time Δ for the two diffusion gradient blocks are assumed to be identical, and the interval between the end of the first and the beginning of the second block is characterized by a mixing time τ. The gradient strengths for the first and second blocks are g and g', respectively, and their corresponding b-values are defined as $b \equiv (\gamma\delta g)^2(\Delta - \delta/3)$ and $b' \equiv (\gamma\delta g')^2(\Delta - \delta/3)$, where γ is the proton gyromagnetic ratio. The 3D diffusion wave vectors for the first and second blocks are $\mathbf{q} \equiv \gamma\delta g\mathbf{n}/2\pi$ and $\mathbf{q}' \equiv \gamma\delta g'\mathbf{n}'/2\pi$, respectively. Here $\mathbf{n}$ and $\mathbf{n}'$ are the standard 3D unit vectors associated with the corresponding diffusion wave vector.

The pair of diffusion wave vectors $(\mathbf{q}, \mathbf{q}')$ can be regarded as a single 6D diffusion wave vector $\tilde{\mathbf{q}} \equiv (\mathbf{q}, \mathbf{q}')$, whereby the first three components of $\tilde{\mathbf{q}}$ correspond to $\mathbf{q}$ and the last three components of $\tilde{\mathbf{q}}$ correspond to $\mathbf{q}'$. The 6D unit vector associated with the direction of $\tilde{\mathbf{q}}$ is $\tilde{\mathbf{n}} \equiv \tilde{\mathbf{q}}/\tilde{q}$, where $\tilde{q} \equiv |\tilde{\mathbf{q}}|$. The 6D b-value of a d-PFG sequence is then given by $\tilde{b} \equiv (2\pi\tilde{q})^2(\Delta - \delta/3) = b + b'$. The logarithm of the d-PFG signal magnitude $\tilde{S}(\tilde{b}, \tilde{\mathbf{n}})$ can be expanded in powers of $\tilde{b}$ as

$$\ln \frac{\tilde{S}\left(\tilde{b}, \tilde{\mathbf{n}}\right)}{\tilde{S}_0} = -\tilde{b}\tilde{D}(\tilde{\mathbf{n}}) + \frac{1}{6}\tilde{b}^2\tilde{D}(\tilde{\mathbf{n}})^2\tilde{K}(\tilde{\mathbf{n}}) + O\left(\tilde{b}^3\right), \tag{1}$$

where $\tilde{D}(\tilde{\mathbf{n}})$ and $\tilde{K}(\tilde{\mathbf{n}})$ are the 6D directional diffusivity and diffusional kurtosis, respectively, and $\tilde{S}_0 \equiv \tilde{S}(0, \tilde{\mathbf{n}})$ is the d-PFG signal magnitude without diffusion weighting. Note that a tilde is used to indicate 6D quantities.

The relationships between the 6D diffusion tensor $\tilde{\mathbf{D}}$ and diffusional kurtosis tensor $\tilde{\mathbf{W}}$, and the corresponding 6D directional diffusivity and diffusional kurtosis are

$$\tilde{D}(\tilde{\mathbf{n}}) = \sum_{\alpha,\,\beta=1}^{6} \tilde{n}_\alpha \tilde{n}_\beta \tilde{D}_{\alpha\beta}, \tag{2}$$

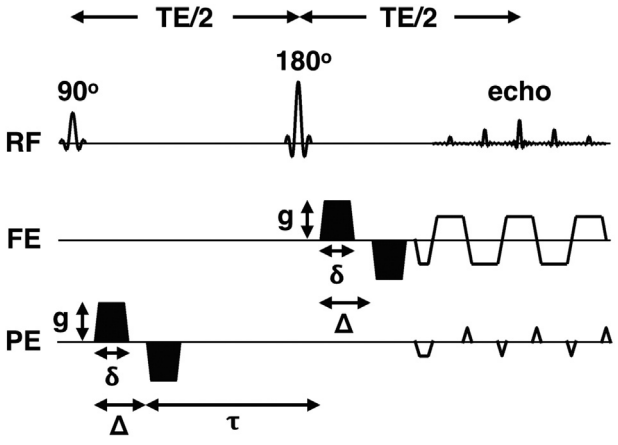

Fig. 1. The pulse sequence diagram of the current d-PFG implementation using a spin-echo echo-planar imaging sequence, consisting of a first block of diffusion gradients applied before the 180° RF pulse and a second block of diffusion gradients applied after the 180° RF pulse. The diffusion gradient strength g, duration δ and diffusion time Δ of both blocks are set to be identical. A mixing time τ separates the end of the first block and the beginning of the second block. The first and second blocks are applied along the phase encoding (PE) and frequency encoding (FE) directions, respectively.