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Separating blood and water: Perfusion and free water elimination from diffusion MRI in the human brain

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ABSTRACT

The assessment of the free water fraction in the brain provides important information about extracellular processes such as atrophy and neuroinflammation in various clinical conditions as well as in normal development and aging. Free water estimates from diffusion MRI are assumed to account for freely diffusing water molecules in the extracellular space, but may be biased by other pools of molecules in rapid random motion, such as the intravoxel incoherent motion (IVIM) of blood, where water molecules perfuse in the randomly oriented capillary network. The goal of this work was to separate the signal contribution of the perfusing blood from that of free-water and of other brain diffusivities. The influence of the vascular compartment on the estimation of the free water fraction and other diffusivities was investigated by simulating perfusion in diffusion MRI data. The perfusion effect in the simulations was significant, especially for the estimation of the free water fraction, and was maintained as long as low *b*-value data were included in the analysis. Two approaches to reduce the perfusion effect were explored in this study: (i) increasing the minimal *b*-value used in the fitting, and (ii) using a three-compartment model that explicitly accounts for water molecules in the capillary blood. Estimation of the model parameters while excluding low *b*-values reduced the perfusion effect but was highly sensitive to noise. The three-compartment model fit was more stable and additionally, provided an estimation of the volume fraction of the capillary blood compartment. The three-compartment model thus disentangles the effects of free water diffusion and perfusion, which is of major clinical importance since changes in these components in the brain may indicate different pathologies, i.e., those originating from the extracellular space, such as neuroinflammation and atrophy, and those related to the vascular space, such as vasodilation, vasoconstriction and capillary density. Diffusion MRI data acquired from a healthy volunteer, using multiple *b*-shells, demonstrated an expected non-zero contribution from the blood fraction, and indicated that not accounting for the perfusion effect may explain the overestimation of the free water fraction evinced in previous studies. Finally, the applicability of the method was demonstrated with a dataset acquired using a clinically feasible protocol with shorter acquisition time and fewer *b*-shells.

Introduction

Diffusion MRI is a method that can provide insight into the microstructural environment of tissue, by sensitizing the signal to the displacement of water molecules (Le Bihan, 2003). At the typical time scales of diffusion MRI experiments, the displacement is highly influenced by the surrounding cellular microstructural environment, which is characterized by the degree to which it hinders or restricts the displacement. Free water is defined as molecules that are neither hindered nor restricted in their movement. Therefore, free water in diffusion MRI exhibits isotropic diffusion with an apparent diffusion coefficient (ADC) of approximately 3 $\mu m^2/ms$ at body temperature

Abbreviations: IVIM, intravoxel incoherent motion; ADC, apparent diffusion coefficient; CSF, cerebrospinal fluid; DTI, diffusion tensor imaging; FA, fractional anisotropy; RD, radial diffusivity; AD, axial diffusivity; SNR, signal-to-noise ratio; MD, mean diffusivity; ROI, region of interest

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(Mills, 1973; Holz et al., 2000). In a typical diffusion MRI acquisition the diffusion time is around 40–60 ms, which imposes that free water is found in large spaces of a few tens of microns, that could only be found in parts of the extracellular space (Pasternak et al., 2012). Accordingly, intracranial free water in the brain can be found as cerebrospinal fluid (CSF) in the ventricles and around the brain parenchyma. However, free water can also, to a smaller extent, be found as CSF and interstitial fluid in the extracellular space of gray and white matter (Pasternak et al., 2009).

When a voxel contains both brain tissue and free-water, the free water component increases the signal attenuation, causing so-called "CSF contamination" that biases the estimation of diffusivities (Pasternak et al., 2009; Metzler-Baddeley et al., 2012a). Recent diffusion MRI methods, such as free water imaging (Pasternak et al., 2009), NODDI (Zhang et al., 2012), AxCaliber (Barazany et al., 2009) and diffusion basis spectrum imaging (Wang et al., 2011), have proposed compartmental models to eliminate CSF contamination by explicitly adding a compartment that accounts for the extracellular free water. These models estimate the free water signal fraction (f_w), which is the relative signal contribution of free water in each voxel. The f_w parameter provided meaningful clinical information, since it allows monitoring of extracellular changes, which could be related to neuroinflammation and/or atrophy in, for example, normal aging (Metzler-Baddeley et al., 2012a), schizophrenia (Pasternak et al., 2012; Pasternak et al., 2016), mild cognitive impairment and Alzheimer's disease (Berlot et al., 2014; Metzler-Baddeley et al., 2012b; Maier-Hein et al., 2015), Parkinson's disease (Ofori et al., 2015), and traumatic brain injuries (Pasternak et al., 2014). Therefore, it is of interest to ensure that the f_w parameter is correctly estimated.

One of the factors that may limit the specificity of f_w to the diffusion of extracellular water molecules is blood perfusion, i.e., the fast displacement of water molecules that are flowing in the blood. While blood flow in large vessels dephases quickly, blood flow that occurs in randomly oriented capillary vessels appears as intra-voxel incoherent motion (IVIM), which includes both diffusion and perfusion (Le Bihan et al., 1986; Bihan et al., 1988). In a diffusion MRI experiment, perfusion has the same effect as fast isotropic diffusion, often referred to as pseudo-diffusion, with an ADC much higher than that of free water. The corresponding fast attenuation of the perfusing blood affects the diffusion signal at low b-values. Accordingly, existing methods to estimate perfusion-related parameters typically acquire low b-value data (e.g., $b < 200$ s/mm^2) to estimate the capillary blood fraction (f_b), which provides a useful measure for brain studies (Le Bihan et al., 1986; Wirestam et al., 2001; Federau et al., 2012; Federau et al., 2014a; Togao et al., 2016) that under certain assumptions can be a surrogate marker for cerebral blood volume (CBV) (Wirestam et al., 2001; Le Bihan and Turner, 1992). CBV is an important parameter for characterizing cerebral hemodynamics, complementing measures of cerebral blood flow (CBF), which can be obtained by dynamic susceptibility contrast (DSC) MRI (Rosen et al., 1990) or arterial spin labeling (ASL) (Dixon et al., 1986; Calamante et al., 1999). CBV measures can also be obtained from dynamic susceptibility contrast MRI (DSC-MRI) (Rosen et al., 1990), or from dynamic contrast-enhanced (DCE) MRI (Sourbron and Buckley, 2013). However, DSC-MRI and DCE-MRI are invasive, since the injection of a contrast agent is required. In addition, these methods require a correctly measured arterial input function, which is difficult to achieve (Federau et al., 2012).

Typically, diffusion MRI sequences include b-values in the order of 1000 s/mm^2 but not low b-values, leading to the misconception that the experiment is not affected by perfusion. However, quantitative diffusion experiments always require the acquisition of at least one more b-value, with the majority of experiments collecting a b=0 volume (or alternatively a very low-b volume) since it yields the largest contrast. The signal, S_0, of this b=0 volume includes contributions from all water pools, regardless of how fast their random motions are. The inclusion of a b=0 volume is, therefore, the source of a potential perfusion effect on a diffusion MRI experiment (Padhani et al., 2009).

In this study, the aim was to show the effects of perfusion on the estimation of the two-compartment free water imaging model, using simulations and real data. We study the effect of perfusion on the estimation of f_w and other diffusivities, with different acquisition schemes that either include or do not include low b-values. We test an approach to eliminate the effect of perfusion on the estimation of f_w by increasing the minimal b-value, from the typical b=0, to a b-value for which the perfusion contribution is minimal. Finally, a three-compartment model for both the perfusion effect and free water is considered. This three-compartment model disentangles the effects of free water diffusion and perfusion, which is of major clinical importance since changes in these components in the brain may indicate different pathologies, i.e., those originating from the extracellular space, such as neuroinflammation and atrophy, and those related to the vascular space, for example, vasodilation, vasoconstriction and capillary density.

Material and methods

Models for diffusion and perfusion

The effect of perfusion on the estimation of f_w was evaluated using simulations and real data, considering models with one, two and three compartments. The single compartment diffusion tensor imaging (DTI) model describes the diffusion weighted signal with a monoexponential signal decay (Basser et al., 1994):

$$S_i = S_0 e^{-b_i \mathbf{g}_i^T \mathbf{D_t} \mathbf{g}_i}, \quad (1)$$

where S_0 is the non-weighted signal, $\mathbf{D_t}$ is a diffusion tensor, and S_i is the diffusion-weighted signal obtained with the i$^{\text{th}}$ applied gradient that has b-value b_i and gradient direction $\mathbf{g}_i$.

The two-compartment free water model (Pasternak et al., 2009; Pasternak et al., 2012; Hoy et al., 2014) describes the diffusion weighted signal as:

$$S_i = S_0 [f_w \cdot e^{-b_i D_w} + (1 - f_w) \cdot e^{-b_i \mathbf{g}_i^T \mathbf{D_t} \mathbf{g}_i}]. \quad (2)$$

This model extends the one compartment diffusion tensor imaging (DTI) model (Basser et al., 1994), by adding a second compartment that represents free water. The free water compartment assumes a fixed diffusivity, D_w=3 μm^2/ms, and therefore this model adds only one new parameter to the DTI model, i.e., the fractional volume of the free water compartment, f_w, with values in the interval [0, 1]. The other compartment accounts for brain tissue, where water molecules are either hindered or restricted, and is modeled using a diffusion tensor $\mathbf{D_t}$ (Basser et al., 1994; Stejskal and Tanner, 1965). The eigenvalues of $\mathbf{D_t}$ can be used to calculate fractional anisotropy (FA), radial diffusivity (RD), and axial diffusivity (AD), which are all corrected for free water contents.

Similar to the free water model, the IVIM model has two compartments, with one of the compartments modeling diffusivity in tissue (Bihan et al., 1988). However, in the IVIM model the additional compartment reflects the signal from the vascular components. Specifically, it is assumed that water molecules flow in the blood in a randomly oriented sub-voxel network of capillaries, which is modeled as pseudo-diffusion with a diffusivity that is higher than that of water molecules in the parenchyma (Bihan et al., 1988):

$$S(b) = S_0 (f_b \cdot e^{-b(D_b + D^*)} + (1 - f_b) \cdot e^{-bD_t}). \quad (3)$$

Here, D_t is the mean diffusivity in tissue, originally assumed to be isotropic and hence described as a scalar. D_b is the mean diffusivity in blood, and D^* is the pseudo-diffusion coefficient, which represents the additive mobility of water molecules due to the perfusion in the randomly oriented capillaries. Since the water molecules in the capillary blood are considered to experience both diffusion and