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T_1 relaxometry of crossing fibres in the human brain

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ABSTRACT

A comprehensive tract-based characterisation of white matter should include the ability to quantify myelin and axonal attributes irrespective of the complexity of fibre organisation within the voxel. Recently, a new experimental framework that combines inversion recovery and diffusion MRI, called inversion recovery diffusion tensor imaging (IR-DTI), was introduced and applied in an animal study. IR-DTI provides the ability to assign to each unique fibre population within a voxel a specific value of the longitudinal relaxation time, T_1, which is a proxy for myelin content. Here, we apply the IR-DTI approach to the human brain in vivo on 7 healthy subjects for the first time. We demonstrate that the approach is able to measure differential tract properties in crossing fibre areas, reflecting the different myelination of tracts. We also show that tract-specific T_1 has less inter-subject variability compared to conventional T_1 in areas of crossing fibres, suggesting increased specificity to distinct fibre populations. Finally we show in simulations that changes in myelination selectively affecting one fibre bundle in crossing fibre areas can potentially be detected earlier using IR-DTI.

Introduction

White matter (WM) is organised in bundles of axons, myelinated to a varying degree, connecting specific areas of the brain. Axons tend to group into fascicles and appear to prefer to fasciculate with axons of their own type (Zipser et al., 1989); as a result, tracts consisting primarily of a homogeneous population of axons are generated (Bray et al., 1980; Kapfhammer et al., 1986; Kröger and Walter, 1991).

MRI techniques have proven to be an invaluable tool to characterise brain WM non-invasively in recent years. Rather than searching for the single MRI technique that best describes the structure of WM, there is increasing interest in multi-modal approaches, which combine different MRI techniques sensitive to distinct aspects of WM. An example is *Tractometry* (Bells et al., 2011), where the authors proposed a strategy to achieve a comprehensive multi-modal quantitative assessment of WM along specific tracts. Diffusion tensor MRI (DT-MRI) (Basser et al., 1994) allows estimation of biomarkers that reflect largely axonal properties, but are also modulated by myelin content (Beaulieu, 2002). The CHARMED approach (Assaf and Basser, 2005; Assaf et al., 2004) models water diffusion inside the axon separately from that outside the axon, providing a proxy measure of axonal density, which has been shown to correlate well with the total myelin content (De Santis et al., 2014). Q-space diffusion MRI parameters (Callaghan et al., 1990) have also been linked to the degree of myelination in recent work (Anaby et al., 2013). Myelin is believed to be an important source of contrast in T_2^*-weighted images from WM at high field (Lee et al., 2012; Sati et al., 2013). In addition, the longitudinal relaxation time T_1 is believed to be mostly sensitive to myelin content in both WM (De Santis et al., 2014; Mottershead et al., 2003; Thiessen et al., 2013) and gray matter (Lutti et al., 2013; Stüber et al., 2014), although other factors (e.g., oedema, gliosis and axon density) affect this contrast too. MRI-based methods specific for myelin quantification have also been developed, including multi-component relaxometry (Deoni et al., 2008; MacKay et al., 1994) and quantitative magnetisation transfer imaging (Ramani et al., 2002; Sled and Pike, 2000).

With the development of more sophisticated diffusion-based approaches to reconstruct WM fibre architecture (e.g., Tournier et al. (2004), Tuch (2004), Wedeen et al. (2008)), the practice of characterising WM structure for each tract, rather than for each voxel,

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has become more commonplace. Since between 60 and 90% of the WM voxels contain complex fibre architecture that can no longer be described by a single WM fibre population (Jeurissen et al., 2012), it is necessary to apply techniques that are capable of resolving crossing fibres within the voxel, to provide tract-specific measures. If the aforementioned hypothesis that axonal bundles are structurally homogeneous holds, this is expected to increase biological specificity and to facilitate the detection of tract-specific properties, and their changes under learning, development and disease in conditions affecting only one population out of many crossing in the same voxel. While several methods have been proposed to assign distinct diffusion properties to distinct fibre populations, e.g. fibre-specific axonal density (Assaf and Basser, 2005; Assaf et al., 2004), orientational anisotropy (Dell'acqua et al., 2012), apparent fibre density (Raffelt et al., 2012) and axonal diameter (Zhang et al., 2011), methods developed to quantify myelin to date provide only a single (i.e., average) myelin content of the voxel, irrespective of the architectural paradigm.

Recently, a new MRI technique combining inversion recovery and diffusion, called IR-DTI, was introduced to provide fibre-specific estimates of the relaxation time T_1 and of the diffusion tensor (Barazany and Assaf, 2012; De Santis et al., 2015). This technique was applied to fixed tissue of an animal model, showing the ability to provide tract-specific values of T_1 in crossing areas, reflecting differential myelination properties. Here, we apply this technique in vivo to the human brain for the first time. Specifically, our aims are: 1) to prove feasibility of IR-DTI for human applications; 2) to characterise tract profiles using tract-specific values for T_1; 3) to compare IR-DTI to conventional T_1 measures in their ability to discriminate multiple T_1s in a voxel; and 4) to compare the sensitivity to tract specific T_1 *changes* of IR-DTI to that of conventional single T_1 maps in areas of crossing fibres.

Methods

Model

Conventional inversion recovery (IR) fits a single relaxation time T_1 for each voxel, according to:

$$S/S0 = 1 - 2 \cdot \exp\left(-TI/T_1^{IR}\right) \quad (1)$$

If the voxel is composed of more than one T_1 component, it is in principle possible to perform a multi-exponential fit on the same IR data, e.g., according to:

$$S/S0 = \sum_i f_i \cdot \left[1 - 2 \cdot \exp\left(-TI/T_1^i\right)\right] \quad (2)$$

where i is the number of T_1 components. However, separating two or more exponential decays with similar rates may be very difficult, because of well recognised difficulties (Touboul et al., 2005).

IR-DTI instead provides the possibility of recovering multiple relaxation times within a voxel by exploiting the orientational dependence of the diffusion signal. The IR-DTI protocol comprises several inversion recovery-prepared diffusion MRI series acquired for different inversion times (TI). The combined contrast is described by the following equation (De Santis et al., 2015):

$$S/S0 = \sum_i f_i \cdot \left[1 - 2 \cdot \exp\left(-TI/T_1^i\right)\right] \cdot \exp\left(-bg^T D_i g\right) \quad (3)$$

The IR-DTI signal is modelled as a summation over i populations, each characterised by a volume fraction, f_i, a specific diffusion tensor D_i and a specific T_1^i. In the original implementation, two populations were fitted in each voxel of the rat brain. To account for more complex fibre arrangements found in human WM, and to avoid overfitting in areas of coherent orientation, here a model selection strategy is applied to decide how many compartments should be fitted voxel-to-voxel, based on Jeurissen et al. (2012).

Simulations

Simulations were used to test the capability of IR-DTI to disentangle multiple components in a crossing fibre voxel and to compare it with conventional IR. Eq. (3) was simulated using two different geometries: two crossing fibres, oriented along x- and y-axis, associated with T_1s of 800 and 1000 ms respectively, and three crossing fibres, oriented along x-, y- and z-axis, associated with T_1s of 800, 1000 and 1200 ms respectively. The fibres had identical diffusion properties (diffusion parallel to the fibre $D = 1.3 * 10^{-3} mm^2/s$), but had different volume fraction (0.4 and 0.6 in case of two fibres, 0.26, 0.33 and 0.41 in case of three fibres respectively). In addition, the angle between the first two fibres was changed in the range 30°–90°. The scheme used had the following parameters: TI = 175, 250, 300, 350, 400, 450, 500, 585, 675, 750, 850, 1100, 1500 ms, 15 non-collinear gradient orientations plus 2 unweighted scans for each TI for a total of 221 measurements, $b = 1000\ s/mm^2$. 100,000 noisy repetitions were generated adding noise to generate Rician-distributed data at signal-to-noise ratio (SNR) = 20 in the unweighted scan, which is a conservative estimate of the SNR achievable in vivo (see Section Data processing). Eq. (1) for two fibres, associated with T_1s of 800 and 1000 ms, respectively, was simulated using the same total number of measurements (221), the same TI range (175–1500ms, 221 equally-spaced datapoints), the same number of repetitions (i.e. 221 measurements) and the same SNR, but without diffusion weighting. IR-DTI data were fitted to Eq. (3); the orientational information was assumed to be equal to the true value in the fit, to mirror what is done in vivo (see Section Data processing). IR data were fitted to Eq. (1). To test the minimum effect size needed by IR-DTI and IR to detect a statistically significant T_1 change, the same simulations were repeated for different values of the two T_1s, simulating an increase of up to 10% in the smallest and in the largest T_1, respectively. Data were then fitted to both Eqs. (3) and (1), and the difference with the original value was evaluated. The difference was compared with the variability measured in vivo for the different tracts, reported in Table 2 (see Subsection Statistical analysis).

Data acquisition

7 healthy subjects with no history of neurological diseases participated in the study. Mean age (standard deviation) was 29 ± 6 years; 4 of the participants were males and 3 were females. The experimental procedures were approved by the ethics committee of the Faculty for Psychology and Neuroscience at Maastricht University, and were performed in accordance with the approved guidelines and the Declaration of Helsinki. Informed consent was obtained from each participant before conducting the experiments. To minimise

Table 1
Repetition time, IR-DTI scan duration and total acquisition time (TA) for all subjects.

Subject	TR (s)	IR-DTI duration (min)	Total TA (min)
subj 1	13.5	47	62
subj 2	10.5	37	52
subj 3	14	49	64
subj 4	14	49	64
subj 5	12.5	44	59
subj 6	10	35	50
subj 7	10.5	37	52