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Why diffusion tensor MRI does well only some of the time: Variance and covariance of white matter tissue microstructure attributes in the living human brain ☆

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ABSTRACT

Fundamental to increasing our understanding of the role of white matter microstructure in normal/abnormal function in the living human is the development of MR-based metrics that provide increased specificity to distinct attributes of the white matter (e.g., local fibre architecture, axon morphology, and myelin content). In recent years, different approaches have been developed to enhance this specificity, and the *Tractometry* framework was introduced to combine the resulting multi-parametric data for a comprehensive assessment of white matter properties.

The present work exploits that framework to characterise the statistical properties, specifically the variance and covariance, of these advanced microstructural indices across the major white matter pathways, with the aim of giving clear indications on the preferred metric(s) given the specific research question.

A cohort of healthy subjects was scanned with a protocol that combined multi-component relaxometry with conventional and advanced diffusion MRI acquisitions to build the first comprehensive MRI atlas of white matter microstructure. The mean and standard deviation of the different metrics were analysed in order to understand how they vary across different brain regions/individuals and the correlation between them. Characterising the fibre architectural complexity (in terms of number of fibre populations in a voxel) provides clear insights into correlation/lack of correlation between the different metrics and explains why DT-MRI is a good model for white matter only some of the time. The study also identifies the metrics that account for the largest inter-subject variability and reports the minimal sample size required to detect differences in means, showing that, on the other hand, conventional DT-MRI indices might still be the safest choice in many contexts.

Introduction

Diffusion tensor MRI (DT-MRI) has proven to be an incredibly powerful tool over recent years (Basser, 1995; Basser et al., 1994). Numerous studies have been performed documenting the clinical utility of DT-MRI in various brain diseases (Assaf and Pasternak, 2008) and its ability to track specific patterns in the developing (Hüppi et al., 1998) as well as in the ageing brain (Pfefferbaum et al., 2000). In addition, the ability to recover voxel-wise the orientation of the fibre pathways has widespread implications in the fields of cognitive neuroscience and neurobiology (Ulmer et al., 2005).

To increase the anatomical specificity of DT-MRI, an approach for obtaining 'tract-specific' measurements of tissue microstructure was developed by mapping specific microstructural parameters along pathways reconstructed by tractography (Jones et al., 2005). However, while anatomical specificity can be improved with this approach (compared to voxel-wise estimates), and despite the growing popularity of DT-MRI, the two most-widely reported indices, the fractional anisotropy (FA) and mean diffusivity (MD) (Basser and Pierpaoli, 1996) have a notorious lack of specificity to different sub-components of white matter (WM) microstructure. Axonal membranes play the primary role in determining FA, but myelination also modulates FA (Beaulieu, 2002). Moreover, the fibre architectural paradigm (Pierpaoli et al., 1996) has a huge impact, where intra-voxel orientational dispersion of fibre populations leads to a reduction in the measured anisotropy (Budde and

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Annese, 2013). Finally, water diffusivity parallel to the axon and the axon morphology and density will also modulate FA.

Understanding the role of WM microstructure in brain function in health and disease demands more specific indices that tap into these sub-components. Different approaches have recently been proposed to disentangle the role of the fiber architectural paradigm from the axon morphology. For example, the composite hindered and restricted model of diffusion, or CHARMED (Assaf and Basser, 2005; Assaf et al., 2004), explains the signal as the contribution of two different pools: a hindered extra-axonal compartment and one or more intra-axonal compartments, whose properties are characterised by a model of restricted diffusion perpendicular to fibre axis within impermeable cylinders (Neuman, 1974). This model recovers both the fibre arrangements and distinct axon-specific parameters, e.g., the restricted fraction (RF), sometimes interpreted as axonal density, and the intra-axonal longitudinal diffusivity (IAD), holding great promise for increasing the specificity of diffusion MRI. For example, CHARMED indices have been shown to be more sensitive than DT-MRI in characterising tissue changes arising during short term neuro-plasticity (Tavor et al., 2013).

Characterising myelin properties is also crucial for understanding brain function, since myelin serves multiple roles, which include reducing conductive leak, reducing charging time of the axonal segment and increasing conduction velocity. Several ways of quantifying the myelin content using MRI have been proposed over recent years (MacKay et al., 1994; Mehta et al., 1996; Sled et al., 2004). An approach that is considered particularly useful, due to its efficiency in term of scan duration, is the multi-component driven equilibrium single pulse observation of T1 and T2, or mcDESPOT analysis (Deoni et al., 2008). McDESPOT produces whole brain maps of the myelin water fraction (MWF) and the intrinsic relaxation times T1 and T2 in a clinically feasible time, i.e. typically less than 10 min on most human MRI scanners.

Combining different microstructural indices for a comprehensive assessment of WM is at the basis of the *Tractometry* philosophy introduced recently (Bells et al., 2011a). This method combines macromolecular measurements from optimized magnetization transfer imaging (Cercignani and Alexander, 2006), multicomponent T2 species from relaxometry (Deoni et al., 2008) and axonal density measurements from CHARMED (Assaf and Basser, 2005) along specific white matter pathways reconstructed from diffusion MRI, providing a comprehensive assessment of multiple microstructural metrics.

The aim of the current work is to deploy the *Tractometry* approach in a cohort of healthy participants and extract the mean and standard deviation of the different microstructural indices, in order to understand how they vary across different brain regions/individuals, the correlation between them and their statistical power in detecting differences between groups.

Specific goals are: 1) to create an atlas of axon-specific characteristics measuring CHARMED metrics, conventional DT-MRI indices, the myelin water fraction and the relaxation times T1 and T2; 2) to investigate correlations between the different metrics and find the indices that account for the largest variability; and 3) to evaluate the minimal group size required to detect a true difference in means at a predefined probability using a statistical power analysis (Maxwell et al., 2008).

We report mean values and confidence intervals of multi-variate data for a number of major white matter fasciculi. To capture salient characteristics of the microstructural indices and to compare the trends for the different tracts irrespectively of their length/width, the parameters are also projected along the tract profile. We explain the correlations between the different metrics in terms of the underlying fibre architecture. In addition, we identify the indices that account for the largest inter-subject variability and evaluate the minimal sample size required to detect differences in means, with the aim of ensuring that future studies are sufficiently powered to detect effects robustly. The information gained is used to speculate about the most appropriate metrics to be used, suggesting that DT-MRI is the best choice for characterising white matter microstructure only some of the time.

Materials and methods

Data acquisition

Seventeen healthy right-handed participants (mean age/standard deviation = 24.2/2.8 y) were included in this study. Informed consent was obtained prior to scanning and the study was performed with approval from the local ethics review board. MRI data were acquired on a 3 T General Electric HDx MRI system (GE Medical Systems, Milwaukee, WI) using an eight channel receive only head RF coil.

The MRI protocol comprised: cardiac-gated DT-MRI protocol (TE = 87 ms, 45 gradient orientations (Jones et al., 1999), b-value = 1200 s/mm^2, spatial resolution (SR) 1.9 × 1.9 × 2.4 mm, total acquisition time (AT) ~20 min depending on the heart rate), CHARMED protocol (TE/TR = 114/17000 ms, 130 gradient orientations distributed on 8 shells, maximum b-value = 7500 s/mm^2, SR 2.4 isotropic, AT 35 min) (De Santis et al., in press), mcDESPOT protocol (spoiled gradient recalled, or SPGR, acquisitions: TE/TR = 2.1/4.7 ms, flip angles = [3, 4, 5, 6, 7, 9, 13, 18°]; balanced Steady-State Free Precession, or bSSFP, acquisitions: TE/TR = 1.6/3.2 ms, flip angles = [10.6, 14.1, 18.5, 23.8, 29.1, 35.3, 45, 60°], SR 2.4 isotropic, AT 10 min) (Deoni et al., 2008), and high resolution T1-weighted anatomical scan (FSPGR). bSSFP acquisitions were repeated with and without 180 RF phase alteration to remove SSFP banding artefacts, B0 and B1-induced errors in the derived myelin water fraction estimates (Deoni, 2011).

Data analysis

DT-MRI analysis was performed with *ExploreDTI* (Leemans et al., 2009) to obtain FA, MD, AD and RD maps (fractional anisotropy, mean diffusivity, axial and radial diffusivity, respectively). Whole brain tractography was obtained for each subject in native space using constrained spherical harmonic deconvolution (Tournier et al., 2004). Track termination was based on a fibre orientation density amplitude threshold of 0.1.

Waypoints were then defined to virtually dissect (Catani et al., 2002) the cingulum, arcuate, uncinate, superior longitudinal, inferior longitudinal, inferior fronto-occipital, fornix and thalamo-cortical fasciculi in each hemisphere. A binary map was computed for each reconstructed fasciculus, with the same matrix size as the FA, but taking a value of one in each voxel intersected by a streamline, zero elsewhere.

CHARMED data were corrected for motion and distortions using a previously-reported CHARMED-specific registration routine (Ben-Amitay et al., 2012). An in-house program coded in Matlab (The MathWorks, Natick, MA) was used to calculate CHARMED parameters RF and IAD (restricted fraction and intra-axonal diffusivity, respectively) according to De Santis et al. (2013). Using a model selection approach (De Santis et al., in press), the number of predominant fibre orientations present in the voxel was obtained.

SPGR and bSSFP images for each participant were corrected for motion using FMRIB's Linear Image Registration Tool (Jenkinson and Smith, 2001) to the first acquired image; maps of MWF, T1 and T2 (the myelin water fraction and the intrinsic relaxation times T1 and T2, respectively) were obtained fitting the mcDESPOT model using a script coded in C++ (Deoni et al., 2008).

DT-MRI, CHARMED and mcDESPOT parameters were corrected for partial volume effects due to CSF contamination (Bells et al., 2011b; Pasternak et al., 2009).

Tract reconstruction and normalisation

For each subject, all the parametric maps were non-linearly registered to the T1-weighted anatomical scan using the FNIRT routine from the FSL package (Jenkinson et al., 2012) to remove EPI distortions. The latter was used to normalize the brain in MNI space again via non-