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Diffusion imaging of reversible and irreversible microstructural changes within the corticospinal tract in idiopathic normal pressure hydrocephalus

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ABSTRACT

The symptoms of idiopathic normal pressure hydrocephalus (iNPH) can be improved by shunt surgery, but prediction of treatment outcome is not established. We investigated changes of the corticospinal tract (CST) in iNPH before and after shunt surgery by using diffusion microstructural imaging, which infers more specific tissue properties than conventional diffusion tensor imaging. Two biophysical models were used: neurite orientation dispersion and density imaging (NODDI) and white matter tract integrity (WMTI). In both methods, the orientational coherence within the CSTs was higher in patients than in controls, and some normalization occurred after the surgery in patients, indicating axon stretching and recovery. The estimated axon density was lower in patients than in controls but remained unchanged after the surgery, suggesting its potential as a marker for irreversible neuronal damage. In a Monte-Carlo simulation that represented model axons as undulating cylinders, both NODDI and WMTI separated the effects of axon density and undulation. Thus, diffusion MRI may distinguish between reversible and irreversible microstructural changes in iNPH. Our findings constitute a step towards a quantitative image biomarker that reflects pathological process and treatment outcomes of iNPH.

1. Introduction

Idiopathic normal pressure hydrocephalus (iNPH) is a geriatric disease characterized by the triad of gait disturbance, cognitive impairment, and urinary incontinence (Halperin et al., 2015; Mori et al., 2012). The reported prevalence is 0.51–2.9% in the elderly population (Miyajima et al., 2016). The symptoms of iNPH can be improved by surgery to create a ventriculo-peritoneal or lumbo-peritoneal cerebrospinal fluid (CSF) shunt (Kazui et al., 2015; Miyajima et al., 2016), especially in the early stage of the disease (Bradley, 2015). However, the reported degree of improvement has varied widely among different case series (Halperin et al., 2015; Poca et al., 2005; Solana et al., 2012). Therefore, a quantitative biomarker that reflects disease severity and predicts treatment response has been sought (Ringstad et al., 2016; Virhammar et al., 2014).

Diffusion MRI has revealed valuable insights into many disorders and age-related changes in the central nervous system by providing quantitative measures of neural microstructure, such as fractional anisotropy (FA), in conventional diffusion tensor imaging (DTI) (Abe et al., 2002; Cohen et al., 2017; Sexton et al., 2011; Shizukuishi et al., 2013). Generally, neurological disorders are associated with decreased FA, which has been attributed to pathologies such as white matter degeneration, demyelination, and gliosis. The FA increase within the corticospinal tract (CST) in iNPH is an interesting exception (Hattingen et al., 2010; Hattori et al., 2012; Jurcoane et al., 2014; Kim

Abbreviations: AD, axial diffusivity; AWF, axonal water fraction; CSF, cerebrospinal fluid; CST, corticospinal tract; DTI, diffusion tensor imaging; FA, fractional anisotropy; iNPH, idiopathic normal pressure hydrocephalus; MD, mean diffusivity; NODDI, neurite orientation dispersion and density imaging; ODI, orientation dispersion index; RD, radial diffusivity; ROI, region of interest; VOI, volume of interest; VF, volume fraction; WMTI, white matter tract integrity.

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et al., 2011; Nakanishi et al., 2013; Scheel et al., 2012). This phenomenon distinguishes iNPH from other dementia disorders. The FA increase, which is driven by the increase of axial diffusivity (AD), has been speculated to reflect the stretching of neural fibers due to compression by the enlarged ventricle. The axons undulate in the normal physiological state, and stretching (which reduces undulation) increases FA and AD (Nilsson et al., 2012). A few studies have reported that the increased FA and AD of the CST tend to normalize after shunt surgery (Jurcoane et al., 2014; Kim et al., 2011; Scheel et al., 2012), consistent with recovery from stretching.

The increased FA in the CST in iNPH contrasts with the decrease in FA in areas outside the CST in iNPH and other chronic neurological diseases (Hattori et al., 2012; Scheel et al., 2012); thus, correlating FA with symptom severity or treatment response is difficult. In a previous study, the correlation between CST FA and the severity of gait disturbance in iNPH was weak (Hattingen et al., 2010). We hypothesize that FA within the CST in iNPH reflects a mixture of an increase caused by axon stretching and a decrease caused by neurodegeneration. Although axon stretching is expected to be at least partially reversible, the existence of shunt non-responders indicates that part the neuronal damage in the chronic stage of iNPH is irreversible. Although a correlation between AD of the CST and treatment response has been reported (Jurcoane et al., 2014), relying solely on AD for predicting surgical outcomes is also difficult, because loss of neuronal cells may increase diffusivities in all directions, including AD.

Although FA and other conventional DTI measures are sensitive to many microstructural properties, such as axon density, orientational coherence, and myelination, they are not highly specific to any of these properties (Jones et al., 2013). Towards more specific quantification of brain microstructure, the trend in diffusion MRI is to develop white matter model consisting of several compartments and to estimate the compartment parameters (orientation, volume fraction, diffusivity, etc.) from the measured signals. For example, the composite hindered and restricted water diffusion (CHARMED) model (Assaf and Basser, 2005) represented the intra-cellular compartment as impermeable parallel cylinders with a gamma distribution of radii and the extra-cellular compartment as anisotropic diffusion tensor, and provided sensible maps of axon density in vivo. Subsequently, Alexander et al. introduced minimal model of white matter diffusion (MMWMD) to obtain orientationally-invariant measurement (Alexander et al., 2010). However, the long scan time had been the limitation for clinical application of these techniques. Recently, neurite orientation dispersion and density imaging (NODDI) (Zhang et al., 2012) enabled estimation of the intracellular volume fraction (v_{ic}) and orientation dispersion index (ODI) from a clinically achievable scan, and has been widely used to investigate neurological disorders and normal aging (Cercignani et al., 2017; Colgan et al., 2015; Kamagata et al., 2016; Merluzzi et al., 2016). Typically, a decrease of v_{ic} is interpreted as neuronal loss. Irie et al. reported that a decrease of ODI in the CST was more specific to iNPH than an FA increase (Irie et al., 2017). They also observed that v_{ic} of the CST was lower in patients than in controls, indicating the potential of v_{ic} as a marker of chronic damage in iNPH. In this context, we investigated the postoperative changes of these metrics in the present study. If ODI is specific to stretching and v_{ic} is specific to neuronal loss, ODI should normalize after the surgery, whereas v_{ic} should not.

Currently available methods of diffusion microstructural imaging rely on simplified models, and parameters of interest are occasionally estimated at the cost of introducing constraints that may be invalid. Among the several constraints for NODDI, the assumption of a single, fixed diffusivity for nervous tissue throughout the whole brain (for human in-vivo studies, 1.7×10^{-3} mm^2/s) is especially unrealistic in disease conditions like iNPH. Although simplification is required for achieving clinical practicability in both data acquisition and analyses, we need to recognize the biases. To make our observations more convincing, we compared NODDI with another method, white matter tract integrity (WMTI) (Fieremans et al., 2011), and looked into the consistency of the results. WMTI is not based on fixed diffusivity values, but rather estimates intra- and extra-axonal diffusivities independently. WMTI contains different assumptions and limitations from those of NODDI, as detailed in Section 2.1. Finally, neither NODDI nor WMTI explicitly takes axon undulation into account. Alteration of properties not included in the model can influence the output parameters; for example, neurite beading affects NODDI and WMTI metrics (Skinner et al., 2015). To investigate how stretching and axon density affect the estimated metrics, we carried out Monte-Carlo simulation using undulating cylinders as model of axons.

2. Materials and methods

2.1. Theory

2.1.1. The common basis of NODDI and WMTI

Both NODDI and WMTI rely on the popular overarching model that considers the intra-axonal compartment as “stick”. In other words, they assume the transverse signal attenuation from the intra-axonal space to be zero. This assumption has been supported by several recent studies that reported diffusion measurement with current clinical MR systems are practically insensitive to the transverse signal attenuation from the intra-axonal space (Burcaw et al., 2015; Ning et al., 2017; Novikov et al., 2016a). As detailed in the Sections 2.1.2 and 2.1.3, NODDI and WMTI differ in how they deal with the diffusivities (fixed or estimated), the orientation distribution function (dispersed or coherent), and the number of compartments.

2.1.2. NODDI

NODDI describes the diffusion MRI signal as a sum of three non-exchanging compartments:

$$S = (1-v_{iso})(v_{ic}S_{ic} + (1-v_{ic})S_{ec}) + v_{iso}S_{iso} \quad (1)$$

where S is the entire normalized signal; S_{ic}, $S_{ec,}$ and S_{iso} are the normalized signals of the intracellular, extracellular, and CSF compartments, respectively; and v_{ic} and v_{iso} are the normalized volume fractions of the intracellular and CSF compartments, respectively (Zhang et al., 2012). The intracellular, extracellular, and CSF compartments are modeled as sticks with orientation dispersion, anisotropic Gaussian diffusion (tensor ellipsoids), and isotropic Gaussian diffusion, respectively. NODDI mainly focuses on estimating dispersion and uses a single fixed diffusivity value for both intra- and extra-axonal spaces. NODDI also describes axon orientation distribution with a single Watson distribution, and approximates the extra-axonal transverse diffusivity ($D_{e,\perp}$) as a function of the intracellular volume and parallel diffusivity ($D_{e,\parallel}$, fixed as 1.7×10^{-3} mm^2/s), i.e., as $D_{e,\perp} = D_{e,\parallel}(1-v_{ic})$.

2.1.3. WMTI

The WMTI model (Fieremans et al., 2011) relates diffusional kurtosis imaging metrics (Jensen and Helpern, 2010) to features of white matter microstructure. The intra-axonal volume fraction, also known as the axonal water fraction (AWF), is calculated as:

$$\mathrm{AWF} = \frac{K_{max}}{K_{max}+3} \quad (2)$$

where K_{max} is the maximum kurtosis over all possible directions. The diffusion tensors of the intra- and extra-axonal compartments are derived, with diffusion in the intra- and extra-axonal spaces given by:

$$D_{a,n} = D_n\left[1-\sqrt{\frac{K_n(1-AWF)}{3AWF}}\right], D_{e,n} = D_n\left[1+\sqrt{\frac{K_n \cdot AWF}{3(1-AWF)}}\right] \quad (3)$$

where D_n and K_n are the diffusion and kurtosis, respectively, in a given direction n. The intra-axonal diffusivity parallel to axons (D_a) is