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Myelin volume fraction imaging with MRI☆

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ABSTRACT

MRI is a valuable tool to assess myelin during development and demyelinating disease processes. While multiexponential T_2 and quantitative magnetization transfer measures correlate with myelin content, neither provides the total myelin volume fraction. In many cases correlative measures are adequate; but to assess microstructure of myelin, (e.g. calculate the g-ratio using MRI), an accurate measure of myelin volume fraction is imperative. Using a volumetric model of white matter, we relate MRI measures of myelin to absolute measures of myelin volume fraction and compare them to quantitative histology. We assess our approach in control mice along with two models of hypomyelination and one model of hypermyelination and find strong agreement between MRI and histology amongst models. This work investigates the sensitivities of MRI myelin measures to changes in axon geometry and displays promise for estimating g-ratio from MRI.

1. Introduction

There is a long-standing effort to develop MRI methods that are not just sensitive to myelin but report on changes in myelin with specificity. Recent interest in using MRI to measure the g-ratio (Stikov et al., 2015, 2010; West et al., 2016) has raised the aims of myelin imaging a step further, beyond specificity to accuracy. That is, an ideal method for g-ratio imaging includes more than just a correlative measure of myelin content, but an absolute measure of myelin volume fraction (MVF). To date, two myelin imaging techniques have been particularly well studied: myelin water imaging (MWI) via multi-exponential T_2 (MET_2) analysis (Mackay et al., 1994) and quantitative magnetization transfer (qMT) imaging (Sled and Pike, 2001). Both techniques have been shown to provide correlative measures of myelin content (Laule et al., 2006; Odrobina et al., 2005; Schmierer et al., 2007; Webb et al., 2003), but exactly how each relates to MVF remains unclear.

In the case of MWI, white matter is modeled as being comprised of two micro-anatomically separated water compartments with different transverse relaxation time constants (T_2): 1) water trapped between the lipid bilayers of myelin (myelin water, T_2=5–40 ms, depending on static field strength, B_0), and 2) water in both the intra- and extra-axonal spaces (i/e water, T_2=30–100 ms, depending on B_0). Given sufficient signal-to-noise ratio (SNR), multiple spin-echo amplitudes can be fitted to a model that distinguishes these water pools based on T_2, and the myelin water fraction (MWF) is typically reported as a measure of relative myelin content (Mackay et al., 1994; Menon et al., 1992; Whittall et al., 1997).

Measures of MWF have been shown to correlate with optical density in luxol fast blue stained sections of cadaver brain from MS patients (Laule et al., 2006) and with direct measures of myelin cross sectional area in electron microscopy of control and injured rat nerve (Odrobina et al., 2005; Webb et al., 2003). Also, Laule et al., used literature values of the composition of white matter to predict MWFs that were in close agreement with their observed values (Laule et al.,

Abbreviations: MRI, magnetic resonance imaging; MWF, myelin water fraction; BPF, bound pool fraction; $f_{M,T2}$, myelin volume fraction from MWF; $f_{M,MT}$, myelin volume fraction from BPF; MVF, myelin volume fraction; AVF, axon volume fraction; $f_{M,HIST}$, myelin volume fraction from histology; $f_{A,Hist}$, axon volume fraction from histology; CKO, conditional knockout; PBS, phosphate-buffered saline; MidCC, midbody of corpus callosum; GCC, genu of corpus callosum; SCC, splenium of corpus callosum; AC, anterior commissure; $M_{0,x}$, equilibrium magnetization of x; V_x, volume of x [ml]; C_x, molar concentration of ^{1}H in x [mol ^{1}H / ml]; ρ_x, density of x [g/ml]; ζ_x, molar mass of ^{1}H in x [g / mol ^{1}H]; $w_{x,y}$, mass fraction of x in y [g_x/g_y]; $\Phi_{x,y,}$, volume fraction of x in y [ml_x/ml_y]

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2004). However, none of these studies attempted to explicitly estimate and/or validate values of MVFs from MWF measures. The relationship between MWF and MVF depends on the relative water proton densities in the myelin and non-myelin compartments, but may also depend on the rate at which water exchanges between these compartments (Zimmerman and Brittin, 1957). Studies in rat spinal cord have indicated that variations in MWFs between different white matter tracts may be due to differences in water exchange rates, mediated by variations in axon diameter and myelin thickness (Dula et al., 2010; Harkins et al., 2012). This effect has been postulated to exist in brain (Russell-Schulz et al., 2013; Sled et al., 2004), but it remains unclear to what extent it effects observed MWF values.

Similar to MWI, the qMT method is based on a two-pool model of protons in white matter, but instead of two anatomically separated pools they are two pools of different molecular origins, water protons and protons bound to macromolecules. Although the bound proton signal is not typically measured directly, the exchange of magnetization between the bound and water protons results in contrast that depends on bound proton concentration (Henkelman et al., 1993; Wolff and Balaban, 1989). Thus, given an appropriate series of images with different MT contrast, the ratio of bound protons to total protons, or bound pool fraction (BPF), can be estimated. Note that, unlike the two-pool model used for MWI, this two-pool model: i) incorporates no anatomical information (both water and bound protons pools are assumed to be well mixed from one anatomical compartment, meaning that myelin is not explicitly part of the model), and ii) is predicated on the exchange of magnetization between the two pools (while the MWI model assumes no exchange of magnetization between the two water pools) (Gochberg and Gore, 2007; Sled and Pike, 2001). The lack of anatomy in the model presents a problem in relating BPF to MVF because bound protons will exist in both myelin and non-myelin regions of the tissue, and there is no reason to believe that all bound protons exchange magnetization with water at the same rate. As in MWI, this raises the question of whether geometric characteristics of axons/myelin contribute to the measured BPF.

Similar to literature on MWF, measures of BPF (or similar/related quantities) have been demonstrated to linearly correlate with MVF as measured by histology in both human cadaver brain (Schmierer et al., 2007) and rodent brain and nerve (Janve et al., 2013; Odrobina et al., 2005; Thiessen et al., 2013; Underhill et al., 2011). Stikov et al. have recently used such a linear correlation to estimate MVF from BPF (Stikov et al., 2015), but otherwise, there has been limited effort in explicitly estimating MVF from estimates from qMT measures.

Using literature information on the composition of white matter, this study proposes analytical expressions for computing estimates of MVF from MET_2 and qMT data. These approaches are applied with high resolution 3D MRI protocols to excised and fixed mouse brains from control mice and three mouse models of abnormal myelination. MRI results are quantitatively evaluated with transmission electron microscopy.

2. Theory

To derive myelin volume measures from MRI, a model of white matter tissue that uses volumes, not just populations, of the different proton pools is presented in Fig. 1. The model includes four proton pools, with volumes of bound and water protons in the myelin ($V_{B,M}$ and $V_{W,M}$, respectively) and non-myelin ($V_{B,NM}$ and $V_{W,NM}$, respectively). The model assumes exchange of longitudinal magnetization between the bound and water protons, enabling qMT analysis, but no exchange of water or magnetization between myelin and non-myelin compartments. The MVF (f_M) by definition is

$$f_M = \frac{V_{B,M} + V_{W,M}}{V_{B,NM} + V_{W,NM} + V_{B,M} + V_{W,M}}. \quad (1)$$

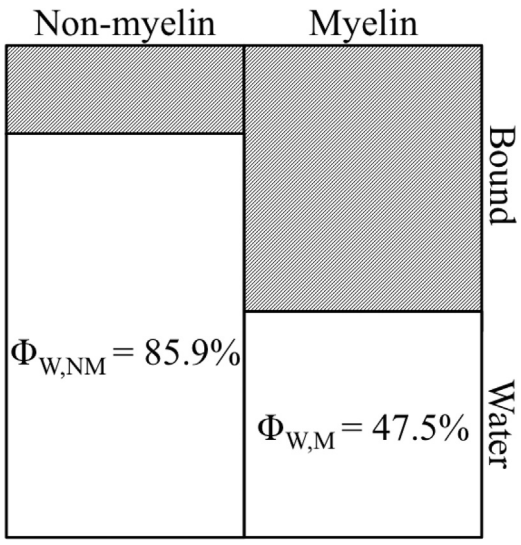

Fig. 1. Volumetric model of white matter. Eqs. (7) and (11) are used to derive accurate myelin volume fractions ($f_{M,T2}$ and $f_{M,MT}$) from MWF and BPF, respectively.

Using the simplifying assumption that molar concentration of protons is equal in all four compartments (see Appendix), magnetization fractions are equal to volume fractions, which permits BPF measured by qMT to be expressed in terms of compartment volume fractions,

$$BPF = \frac{V_{B,NM} + V_{B,M}}{V_{B,NM} + V_{W,NM} + V_{B,M} + V_{W,M}}. \quad (2)$$

Similarly, the myelin water fraction (MWF) measured by MET_2 is

$$MWF = \frac{V_{W,M}}{V_{W,NM} + V_{W,M}} \quad (3)$$

From previous literature (see Appendix), the volume fraction of water in myelin ($\Phi_{W,M}$) is estimated as

$$\Phi_{W,M} = \frac{V_{W,M}}{V_{B,M} + V_{W,M}} = 0.475 \frac{\text{ml } H_2O}{\text{ml tissue}}, \quad (4)$$

and for non-myelin is

$$\Phi_{W,NM} = \frac{V_{W,NM}}{V_{B,NM} + V_{W,NM}} = 0.859 \frac{\text{ml } H_2O}{\text{ml tissue}} \quad (5)$$

Combining Eqs. (1), and (3)–(5), MWF can be written in terms of f_M

$$MWF = \frac{\Phi_{W,M} \times f_M}{\Phi_{W,NM} \times (1 - f_M) + \Phi_{W,M} \times f_M}. \quad (6)$$

which can then be solved to write f_M as a function of MWF,

$$f_{M,T2} = \frac{MWF \times \Phi_{W,NM}}{MWF \times (\Phi_{W,NM} - \Phi_{W,M}) + \Phi_{W,M}}, \quad (7)$$

with the additional "T2" subscript indicating that this is myelin volume fraction as estimated by MET_2 analysis.

For qMT analysis, there is an additional unknown: the volume fraction of the non-myelin bound proton pool, defined here as β.

$$\beta = \frac{V_{B,NM}}{V_{B,NM} + V_{W,NM} + V_{B,M} + V_{W,M}}. \quad (8)$$

Assuming that β were known, and from Eq. (2),

$$[BPF - \beta] = \frac{V_{B,M}}{V_{B,NM} + V_{W,NM} + V_{B,M} + V_{W,M}}, \quad (9)$$

then combining Eqs. (4) and (9), results in