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Adult age differences in subcortical myelin content are consistent with protracted myelination and unrelated to diffusion tensor imaging indices

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ABSTRACT

Post mortem studies suggest protracted myelination of subcortical white matter into the middle age followed by gradual decline in the late adulthood. To date, however, establishing the proposed inverted-U pattern of age-myelin association proved difficult, as the most common method of investigating white matter, diffusion tensor imaging (DTI), usually reveals only linear associations between DTI indices and age among healthy adults. Here we use a novel method of estimating Myelin Water Fraction (MWF) based on modeling the short spin-spin (T_2) relaxation component from multi-echo T_2 relaxation imaging data and assess subcortical myelin content within six white matter tracts in a sample of healthy adults (N=61, age 18–84 years). Myelin content evidenced a quadratic relationship with age, in accord with the pattern observed postmortem studies. In contrast, DTI-derived indices that are frequently cited as proxies for myelination, fractional anisotropy (FA) and radial diffusivity (RD), exhibited linear or null relationships with age. Furthermore, the magnitude of age differences in MWF varied across the white matter tracts. Myelin content estimated by MWF was unrelated to FA and correlated with RD only in the splenium. These findings are consistent with the notion that myelination continues throughout the young adulthood into the middle age. The results demonstrate that single-tensor DTI cannot serve as a source of specific proxies for myelination of white matter tracts.

1. Introduction

Postmortem studies in humans and non-human primates have consistently demonstrated life-span differences in white matter structure, including significant regional variations in myelin content (Kaes, 1907; Yakovlev and Lecours, 1966; Peters, 2002), and multiple alterations appearing in older adulthood, including gliosis, loss of myelin, decreased nodes of Ranvier density and deformation of myelin sheaths (Peters, 2002; Tang et al., 1997). These studies suggest progressive myelination continuing into the fourth decade of life, with cortical association regions exhibiting the starkest differences in myelin content between infancy and middle age (Yakovlev and Lecours, 1966, Kaes, 1907). Furthermore, subcortical and intracortical myelination of sensory-motor brain regions appears to progress faster and decline slower than that of the association areas (Flechsig, 1901; Kaes, 1907).

The obvious limitations of post-mortem studies are impossibility of evaluating changes over time and assessing cognitive performance concurrently with the brain measurements. Therefore, there is a need for accurate, valid and safe methods that would allow gauging brain myelin content *in vivo*. Early studies of age differences in white matter volume suggested non-linear age trends (Bartzokis et al., 2001; Jernigan et al., 2001; Raz et al., 2005; but see Raz et al. (1997, 2004)). Gross volume, however, is a very coarse index of white matter properties, as it reflects contributions of multiple components, and proliferation of some types of them, such as astroglia and microglia as well increased number of myelin sheaths and increased axon diameter may offset the loss of myelin.

The advent of diffusion tensor imaging (DTI, Basser et al., 1994) facilitated assessment of white matter macrostructure through examining the anisotropy of water diffusion in the brain tissue. As myelin constitutes a formidable barrier to diffusion of water molecules, it is plausible that degree of myelination and myelin content can be represented by DTI indices such as fractional anisotropy (FA) and radial diffusivity (RD). Indeed, in several studies, these DTI-derived indices have been linked to myelin content (Gulani et al., 2001; Song et al., 2003) and age differences in RD are

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frequently interpreted as evidence of changes in myelin content (e.g., Lebel et al., 2012). Other DTI-derived indices, such as mean diffusivity (MD, a trace of the diffusion tensor) and axial diffusivity (AD, the principal eigenvalue of the diffusion tensor) are usually not considered proxies for myelin (see Salat (2014) for a review).

To date, life-span age differences in myelination have been inferred predominantly from DTI-based indices, especially RD, which has been interpreted as a marker of myelin integrity in the context of training-related white matter plasticity (Mackey et al., 2012), schizophrenia (Davis et al., 2003), and age-related cognitive decline (Davis et al., 2009). It is important to note, however, that signal from the very short (10–40 ms) component of the spin-spin (T_2) relaxation of water molecules within myelin sheaths is undetected by most DTI studies with TE times that typically exceed 50 ms. The reported validation of DTI indices vis a vis myelin is therefore not only limited to regions of uniform fiber directionality but is insensitive to diffusion of water between myelin sheaths. In recent years, there is a growing awareness that although the DTI-derived indices may be sensitive to myelin presence, these measures are unlikely to serve as specific indicators of myelin content or myelin sheath integrity (Jones et al., 2013).

Although multiple cross-sectional studies revealed significant negative associations between age and FA as well as positive associations between age and RD of the subcortical white matter (see Madden et al. (2012) for a review), in the extant literature, association of age with FA and RD has been described by various functional relationships. In adult life span studies FA evidenced linearly declining, flat or accelerating slope with age and RD showed flat or accelerated age differences (Michielse et al., 2010; Westlye et al., 2010; Hasan et al., 2009). The results of cross-sectional investigations of age differences in FA and RD are inconsistent and, when adults are concerned, do not conform to the patterns of protracted life-span myelination and regional differences suggested by the postmortem studies (e.g., Kaes, 1907). DTI-derived indices lack specificity because FA and RD (as well as AD and MD) reflect multiple structural and organizational properties of the white matter, including axon density and caliber, the intra- and extracellular space, and local geometry of crossing and kissing fibers (Beaulieu, 2002; Jeurissen et al., 2013; Jones et al., 2013; Vos et al., 2012). Moreover, whereas recent longitudinal studies showed significant differential changes in local FA and diffusivity components in a wide age range of healthy adults, the lack of neurobiological specificity of DTI-derived indices significantly constrains interpretation of these findings (Barrick et al., 2010; Sexton et al., 2014; Bender and Raz, 2015; Bender et al., 2016).

Several alternatives have been proposed to overcome the limitations of DTI-based methods in estimating myelin content. A promising method of myelin assessment is the multi-component driven equilibrium single-component observation of T_1 and T_2 (mcDESPOT, Deoni et al., 2008). This approach generates whole-brain maps of T_1, T_2, and myelin fraction by using a combination of spoiled gradient echo recalled (SPGR) and balanced-steady-state free precession (b-SSFP) sequences along with fitting a three-compartment model to the data (Deoni et al., 2013). While whole-brain acquisition with SPGR and b-SSFP sequences is relatively quick, mcDESPOT requires application of multiple flip angles for both sequences (Deoni et al., 2008), which prolongs acquisition times. Moreover, mcDESPOT may be sensitive to magnetization transfer effects (Bieri and Scheffler, 2006; Lenz et al., 2010), tends to over-estimate MWF (Deoni et al., 2008; Zhang et al., 2015) and is yet to be validated by quantitative comparison with direct histological measures of myelin (Deoni et al., 2015).

These limitations can be mitigated by a method that has been developed more than two decades ago (MacKay et al., 1994). This approach relies on the multi-exponential T_2 decay modeling of multi-echo T_2 relaxation imaging data, which directly estimates Myelin Water Fraction (MWF) and thus can provide valid estimates of myelin content. MWF imaging draws on well-known physical properties that determine behavior of water protons within myelin sheaths in magnetic field (Menon and Allen, 1991). Namely, for water trapped between the myelin sheaths the T_2 relaxation time is approximately between 10 and 40 ms (short T_2 component), whereas the T_2 relaxation time of water associated with the intra- and extra-axonal spaces ranges between 60–70 ms (middle T_2 component). These T_2 relaxation components and their relative contribution to the total water signal can be estimated by modeling the multi-exponential decay as a distribution of T_2 components (MacKay et al., 2006; Whittal et al., 1997). Notably, estimates of myelin content derived from MWF have been extensively validated and agree with histological measures of myelin obtained from optical density measurements with luxol fast blue staining (Laule et al., 2006; Laule et al., 2008). In addition, animal models of myelin degeneration (McCreary et al., 2009; Webb et al., 2003) demonstrate sensitivity and utility of MWF in monitoring demyelination and re-myelination. Collectively, these studies provide strong support for the use of MWF imaging for *in vivo* quantification of myelin content. Moreover, recent MRI sequence development has dramatically reduced the acquisition time (Prasloski et al. 2012), thus improving the feasibility of the histologically validated measures of myelin content in humans. To the best of our knowledge, this approach has been used in only one comprehensive study of white matter diffusion properties in 17–70 year old healthy adults (Billiet et al., 2015). That investigation revealed only a few linear as well as quadratic correlations between MWF and age in some regions, and none of these correlations survived a correction for multiple comparisons. Notably, diffusion-based indices in the same sample evidences curvilinear relationship with age in some regions (Billiet et al., 2015). In two other studies that used multi-echo T2 imaging sequences but were not designed to examine age differences, linear increase in MWF with age was observed (Flynn et al., 2003; Lang et al., 2014). Notably, in these two studies, sample age covered the range from early or late childhood to the middle age: 15–55 years (Flynn et al., 2003) and 5–40 (Lang et al., 2014). These studies suggest an increase in MWF values (and, by implication, myelination) into middle age. Thus, the question of age-related differences in regional myelin content requires further study, with a focus on comparison between putative proxies of brain myelin based on multi-T2 component analysis and DTI.

In this study, we had two main objectives. First, we wanted to characterize the age differences in myelin content within selected regions of subcortical white matter in a life-span sample of healthy adults. In accord with the post-mortem evidence, we hypothesized that across adult life span, age would be quadratically related to MWF and this relationship would vary across white matter tracts. Second, we compared age differences in MWF-based estimates with the most commonly reported DTI indices, FA and RD that are frequently taken as indicators of myelination (e.g., Kumar et al., 2014; Lebel et al., 2012; Madden et al., 2012; Song et al., 2003). To avoid adding multiple statistical tests and inflating Type I error, we did not include other DTI –derived indices (AD and MD) that are usually not viewed as proxies for myelin content or integrity. We hypothesized that DTI-based indices, in accord with the extant literature would exhibit linear associations with age. We expected that because of these differences in their associations with age, DTI indices would be unrelated to MWF estimates of myelin content and thus be deemed unsuitable proxies for myelin.