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Age-related microstructural differences quantified using myelin water imaging and advanced diffusion MRI

Thibo Billiet [a,b,c,d,*], Mathieu Vandenbulcke [d,e], Burkhard Mädler [f,g], Ronald Peeters [b,d], Thijs Dhollander [c,h], Hui Zhang [i,j], Sabine Deprez [a,b,c,d], Bea R.H. Van den Bergh [k,l], Stefan Sunaert [a,b,c,d], Louise Emsell [a,b,c,d,e]

[a] Translational MRI, Department of Imaging and Pathology, KU Leuven, Leuven, Belgium
[b] Department of Radiology, University Hospitals Leuven, Leuven, Belgium
[c] Medical Imaging Research Center (MIRC), Leuven, Belgium
[d] Leuven Research Institute for Neuroscience & Disease (LIND), Leuven, Belgium
[e] Department of Old Age Psychiatry, KU Leuven, Leuven, Belgium
[f] Philips Healthcare, Hamburg, Germany
[g] Department of Neurosurgery, Medical Centre, University of Bonn, Bonn, Germany
[h] The Florey Institute of Neuroscience and Mental Health, Melbourne, Victoria, Australia
[i] Department of Computer Science, University College London, London, UK
[j] Centre for Medical Image Computing, University College London, London, UK
[k] Department of Developmental Psychology, Tilburg University, Tilburg, The Netherlands
[l] Department of Psychology, KU Leuven, Leuven, Belgium

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ABSTRACT

Age-related microstructural differences have been detected using diffusion tensor imaging (DTI). Although DTI is sensitive to the effects of aging, it is not specific to any underlying biological mechanism, including demyelination. Combining multiexponential T2 relaxation (MET2) and multishell diffusion MRI (dMRI) techniques may elucidate such processes. Multishell dMRI and MET2 data were acquired from 59 healthy participants aged 17–70 years. Whole-brain and regional age-associated correlations of measures related to multiple dMRI models (DTI, diffusion kurtosis imaging [DKI], neurite orientation dispersion and density imaging [NODDI]) and myelin-sensitive MET2 metrics were assessed. DTI and NODDI revealed widespread increases in isotropic diffusivity with increasing age. In frontal white matter, fractional anisotropy linearly decreased with age, paralleled by increased "neurite" dispersion and no difference in myelin water fraction. DKI measures and neurite density correlated well with myelin water fraction and intracellular and extracellular water fraction. DTI estimates remain among the most sensitive markers for age-related alterations in white matter. NODDI, DKI, and MET2 indicate that the initial decrease in frontal fractional anisotropy may be due to increased axonal dispersion rather than demyelination.

1. Introduction

Throughout adulthood, the human brain undergoes significant biophysical changes in both white matter (WM) and gray matter (GM) (Pannese, 2011). In contrast to nonhuman primates, these maturating and regressive processes occur heterochronically in different brain regions (Haroutunian et al., 2014).

Structural magnetic resonance imaging (MRI) has played a pivotal role in the context of monitoring and understanding the healthy aging process, for example, by measuring atrophy and detecting WM lesions (Fjell et al., 2009; Raz et al., 1997; Salat et al., 2009). However, single-contrast structural MRI is suboptimal for measuring microstructural changes, including myelination, which may predate atrophy (Haroutunian et al., 2014).

Other MRI-based techniques, such as those that are sensitive to the direction of water diffusion (diffusion MRI [dMRI]) or myelin content (relaxometry, magnetization transfer imaging [MTI]), are increasingly being applied to study life span effects. The most widely used of these approaches is diffusion tensor imaging (DTI) (Basser et al., 1994). Fractional anisotropy (FA) describes the degree of nonisotropic diffusion and is a popular, nonspecific DTI metric that is used as a general indicator of microstructural status because of its sensitivity to changes in cell density, size, number, and myelin

* Corresponding author at: Department of Radiology, University Hospitals Leuven, Herestraat 49, Box 7003, B-3000 Leuven, Belgium. Tel.: +32 16 34 90 69; fax: +32 16 34 37 65.
E-mail address: Thibo.billiet@uzleuven.be (T. Billiet).

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status (Beaulieu, 2002; Beaulieu and Allen, 1994). See Tournier et al. (2011) for a review. Age-related differences in FA, mean diffusivity (MD), and radial diffusivity (RD) have been found in various WM regions. The changes are often nonlinear (quadratic) with an initial increase in FA and decrease in MD and RD followed by a reversal that is frequently attributed to deficits in axonal membrane (myelin) integrity. The greatest changes are often found in the anterior corpus callosum (Bartzokis et al., 2012; Brickman et al., 2012; Davis et al., 2009; Inano et al., 2011; Lebel et al., 2012; Pfefferbaum et al., 2000; Salat et al., 2005; Sullivan and Pfefferbaum, 2006).

Although DTI is a popular technique, it is not without significant limitations, many of which relate to the simplicity of the tensor model (Jones and Cercignani, 2010). In response, novel nontensor-based dMRI techniques have been developed. In contrast to DTI, diffusion kurtosis imaging (DKI) also measures non-Gaussian diffusion and may provide additional and complementary information to DTI (Jensen and Helpern, 2010; Jensen et al., 2005). To date, only a few studies have applied this technique to study differences across the life span. In these studies, mean kurtosis (MK), a measure of tissue complexity, was found to increase in WM during maturation and decrease in healthy aging (Coutu et al., 2014; Falangola et al., 2008; Gong et al., 2014; Latt et al., 2013).

Another advanced dMRI analysis technique, neurite orientation dispersion and density imaging (NODDI) (Zhang et al., 2012), aims to quantify the density and dispersion of neurites (i.e., axons and dendrites). These can be seen as independent factors influencing anisotropy and provide a more biologically intuitive model of diffusion changes. NODDI has been successfully applied in previous studies investigating pathologic changes (Billiet et al., 2014; Lally et al., 2014; Winston et al., 2014) and neonates (Jelescu et al., 2015; Kunz et al., 2014; Melbourne et al., 2013) but has not yet been used prospectively in healthy aging.

Diffusion estimates have proven to be sensitive to many microstructural alterations, yet lack specificity. Furthermore, dMRI cannot directly assess myelin, which has an important role in aging processes. Several alternative MRI-based techniques provide myelin markers, including the myelin water fraction (MWF) obtained from multiexponential T2 relaxation (MET2 or myelin water imaging [MWI]) and MTI. Studies using MTI have found evidence of potential age-associated demyelination; yet the lack of specificity of these measures for myelin means that MTI-based findings need confirmation using alternative techniques. In this context, the MWF has superior specificity for myelin content (Stanisz et al., 2004; Vavasour et al., 2011). A few studies have been conducted assessing the evolution of myelination in neonates and children (Deoni et al., 2012; Melbourne et al., 2013; Whitaker et al., 2008), yet limited information exists about the evolution of MET2 metrics during adulthood (Flynn et al., 2003).

There are undisputable, heterogeneous WM microstructural changes associated with aging as assessed using different MRI techniques. However, attributing differences in univariate MRI measures to specific microstructural features is confounded by a lack of specificity and, in the case of novel measures, a lack of studies characterizing their behavior in healthy tissue. In this multimodal MRI study, we therefore aimed to quantify whole-brain and regional age-related differences in both established (DTI) and novel dMRI metrics (DKI, NODDI) as well as in the myelin-specific MET2 technique in a prospective sample of healthy individuals. We contribute valuable normative data for future studies using these techniques and demonstrate the added value of using multiparametric MRI data for assessing age-related WM microstructural changes.

2. Materials and methods

2.1. Participants

Age- and gender-matched healthy volunteers between the ages of 17 and 70 years were recruited through local advertisement in the Leuven University Hospital. Inclusion criteria were the absence of current medical illness, diagnosis of a neurological or psychiatric disorder, previous brain surgery, traumatic brain injury, use of psychotropic medication, and contraindications to MRI scanning. The study was approved by the local ethical committee and conducted in accordance with the Declaration of Helsinki. Originally, 62 volunteers participated of which 59 were retained (minimum age: 17 years, maximum age: 70 years). One data set was discarded because of extensive WM hyperintensities. The remaining participants were free of visible hyperintensities. Two data sets were discarded because of incomplete data acquisition. Participants were randomly scanned within a time frame of 7 months, with the timing of data acquisition distributed evenly across the age range studied. There were slightly more female participants than males (female/male = 36/23), but their mean age did not differ ($t = 0.49$, $p = 0.62$). There was no significant difference in the educational level across the age range investigated ($F = 1.68$, $p = 0.17$). Education level in this instance refers to the highest educational qualification (i.e., most years of education) obtained in Belgium based on 5 levels, which include primary school, secondary school (i.e., high school), higher education of short duration (equivalent to professional bachelor), higher education of long duration (equivalent to professional master), and university degree (academic bachelor + master degree).

2.2. Data acquisition

MRI brain scans were acquired using a 3-T MR scanner (Achieva; Philips, Best, the Netherlands) and a 32-channel phased-array head coil.

2.2.1. Multiexponential T2 relaxation

A 3D GRASE sequence was used to acquire multislice multiecho data of the cerebrum in under 12 minutes (Maedler and MacKay, 2007; Prasloski et al., 2012b). The data consisted of 32 midaxial slices for which 32 echoes were acquired with Δ echo time (ΔTE) = 10 ms (TE = 10, 20, …, 320 ms), repetition time (TR) = 1000 ms, echo-planar imaging readout factor of 3, and voxel size $1 \times 1 \times 2.5$ mm^3.

2.2.2. Diffusion MRI

An echo-planar, multishell, high angular resolution diffusion imaging scheme was used consisting of diffusion-weighted images for b-values of 700, 1000, and 2800 s/mm^2, respectively, applied along 25, 40, and 75 uniformly distributed directions (Poot et al., 2010). Each series of diffusion-weighted images was preceded by a b = 0 image. An additional 7 non−diffusion-weighted images were acquired yielding 10 b = 0 images in total. Constant scan parameters were TR/TE = 7800 ms/90 ms, 50 slices, voxel size $2.5 \times 2.5 \times 2.5$ mm^3, parallel imaging factor 2.

A T1-weighted image was acquired for anatomical reference and image registration purposes using a whole-brain 3D-TFE sequence consisting of 182 contiguous coronal slices with TE = 4.6 ms, TR = 9.6 ms, voxel size $0.98 \times 0.98 \times 1.2$ mm^3. The total scan time of the protocol was approximately 45 minutes.

2.3. Data preprocessing

The main steps in the image processing pipeline are visualized in Fig. 1. After data quality assurance and correction, the MET2 and