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Widespread age-related differences in the human brain microstructure revealed by quantitative magnetic resonance imaging☆

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ABSTRACT

A pressing need exists to disentangle age-related changes from pathologic neurodegeneration. This study aims to characterize the spatial pattern and age-related differences of biologically relevant measures in vivo over the course of normal aging. Quantitative multiparameter maps that provide neuroimaging biomarkers for myelination and iron levels, parameters sensitive to aging, were acquired from 138 healthy volunteers (age range: 19–75 years). Whole-brain voxel-wise analysis revealed a global pattern of age-related degeneration. Significant demyelination occurred principally in the white matter. The observed age-related differences in myelination were anatomically specific. In line with invasive histologic reports, higher age-related differences were seen in the genu of the corpus callosum than the splenium. Iron levels were significantly increased in the basal ganglia, red nucleus, and extensive cortical regions but decreased along the superior occipitofrontal fascicle and optic radiation. This whole-brain pattern of age-associated microstructural differences in the asymptomatic population provides insight into the neurobiology of aging. The results help build a quantitative baseline from which to examine and draw a dividing line between healthy aging and pathologic neurodegeneration.

1. Introduction

Age is the highest risk factor for neurodegenerative disease yet it remains unclear what triggers normal aging processes to diverge into neurodegeneration. In older adults, brain pathology can be present with no apparent cognitive impairment (Fotuhi et al., 2009; Zecca et al., 2004). Macrostructural tissue loss has proved a sensitive marker for neurodegeneration despite having poor pathologic specificity (Barkhof et al., 2009; Benedict and Zivadinov, 2011; Frisoni et al., 2010; McDonald et al., 2009; Scahill et al., 2002). Markers of microstructural changes accompanying atrophy are required to increase sensitivity and specificity (Barkhof et al., 2009; Benedict and Zivadinov, 2011; Frisoni et al., 2010; Noseworthy, 1999; Scahill and Fox, 2007). Our aging population presents a pressing need to disentangle age-related changes from pathologic

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neurodegeneration. This motivated our study in which we examine normal age-related differences and population variance of quantitative magnetic resonance imaging (MRI) parameters that have been shown to reflect underlying differences in the brain microstructure (Dick et al., 2012; Draganski et al., 2011; Freund et al., 2013; Sereno et al., 2013).

Myelin sheaths exhibit degenerative changes with age that reduce conduction velocity (Adinolfi et al., 1991; Aston-Jones et al., 1985) along affected nerve fibers and may explain some of the cognitive decline seen in older adults (Marner et al., 2003; Peters, 2002). The effects of age on myelin are complex because even though some myelin sheaths are seen to degenerate with age, the process of myelin production continues throughout life, though possibly in an uncontrolled or dysfunctional manner (Peters, 2002). Oligodendrocytes are crucial for the production and maintenance of myelin and require iron to sustain their high metabolic rate and facilitate the synthesis of lipids and cholesterol necessary to carry out these functions (Bartzokis, 2011; Connor and Menzies, 1996; Todorich et al., 2009). This makes iron a key co-factor in the production and maintenance of myelin. Iron levels are highly spatially and developmentally heterogenous, increasing rapidly during development with linear increases in later life, even plateauing in some regions (Hallgren and Sourander, 1958). Oligodendrocytes that differentiate later in life produce thinner sheaths that cover a larger number of thinner axons that are more susceptible to functional impairment and destruction (Bartzokis, 2004; Kemper, 1994; Marner et al., 2003; Terao et al., 1994). Over the course of aging, iron accumulates in brain regions that are susceptible to neurodegenerative diseases (Connor et al., 1990; Dexter et al., 1991; Jellinger and Paulus, 1990; Zecca et al., 2004) though it is not wholly clear whether this accumulation is a cause or an effect of degeneration.

Quantitative MRI can circumvent some of the drawbacks of histologic analysis by producing neuroimaging markers for biologically relevant quantities noninvasively. Recent technical developments have enabled in vivo mapping to be performed with high resolution and whole brain coverage (Deoni et al., 2005; Helms and Dechent, 2009; Helms et al., 2008a, 2008b). Macromolecular protons, such as those found in myelin, can be selectively saturated using off-resonance radiofrequency (RF) pulses leading to attenuation of the magnetic resonance (MR) water signal by magnetization transfer (MT) (Wolff and Balaban, 1989). Voxels with a higher macromolecular content will show a greater percentage loss of water magnetization as a consequence of a given pre-pulse (MT saturation). Magnetization transfer measures have been shown to correlate with histologically measured myelin content (Schmierer et al., 2004, 2007), whereas quantitative relaxation rate measurements correlate with iron content (Daugherty and Raz, 2012; House et al., 2007; Langkammer et al., 2010; Rodrigue et al., 2013; Vymazal et al., 1996).

Gaining insight into the multifaceted and inter-dependent biological processes that underlie both aging and neurodegeneration is a complex problem. Here, we use quantitative multiparameter mapping (MPM), which is ideally suited to probe the multiple factors of aging. MPM quantifies the longitudinal relaxation rate, R_1, effective transverse relaxation rate, R_2^*, percent saturation because of MT and effective proton density (PD*). We present a cross-sectional whole brain voxel based quantification (VBQ) analysis of these 4 parameters acquired on a large cohort of healthy volunteers covering a broad age range. We hypothesized that age would correlate with regionally specific reductions in myelin content, changes in iron and water content and ultimately with brain atrophy and that these microstructural changes would be reflected by age-related differences in the MPM data.

2. Methods

2.1. Participants

Participants were recruited from the local university population and by advertising on the departmental website and in local buildings as well as through word of mouth. Potential participants were screened and excluded if they had any of the following: metallic implants, epilepsy, diabetes, history of seizures, neurologic, medical or psychiatric disorders. Of the final pool of participants, all but 2 (1 male, 1 female) were right-handed. To assess cognitive integrity, all older adult participants (60 years or more) additionally underwent a Mini Mental State Examination and achieved scores of 28 or greater. The final cohort consisted of 138 volunteers, of which 49 were men. The group ranged in age from 19 to 75 years with a mean age of 46.6 years and a standard deviation of 21 years. Informed written consent was obtained before scanning.

2.2. Data acquisition

Participants were examined on two 3T whole body MR systems (Magnetom TIM Trio, Siemens Healthcare, Erlangen, Germany, 69 participants per scanner) each equipped with a standard 32 channel head coil for receive and RF body coil for transmission. The data were acquired as part of several cognitive neuroimaging studies at the Wellcome Trust Centre for Neuroimaging with approval from the local ethics committee.

A whole-brain quantitative MPM protocol was used. This consists of 3 spoiled multi-echo 3D fast low angle shot (FLASH) acquisitions with 1 mm isotropic resolution and 2 additional calibration sequences to correct for inhomogeneities in the RF transmit field (Lutti et al., 2010, 2012; Weiskopf et al., 2013). The FLASH volumes were acquired with predominantly proton density (PD), T_1 or MT weighting, determined by the repetition time, and flip angle (α) (repetition time and flip angle were for the PD- and MT-weighted acquisitions: 23.7 ms/6°; and for the T_1-weighted acquisition: 18.7 ms/20°). In the case of the MT-weighted acquisition, a Gaussian RF pulse with 4 ms duration and 220° nominal flip angle was applied 2 kHz off-resonance before nonselective excitation. Gradient echoes were acquired with alternating readout gradient polarity at 6 equidistant echo times between 2.2 ms and 14.7 ms. Two additional echoes were acquired for the PD-weighted acquisition at 17.2 ms and 19.7 ms. A high readout bandwidth of 425 Hz/pixel was used to reduce off-resonance artefacts (Helms and Dechent, 2009). To speed up data acquisition, parallel imaging with a speed up factor of 2 was used in the phase-encoded direction (anterior-posterior) using the generalized auto-calibrating partially parallel acquisition algorithm. A partial Fourier acquisition (6/8 sampling factor) was used in the partition direction (left-right). The total scanning time of the MPM protocol was approximately 25 minutes.

To obtain quantitative maps, the data were processed in the Statistical Parametric Mapping SPM8 framework (Wellcome Trust Centre for Neuroimaging, London) using bespoke MATLAB tools (The Mathworks Inc, Natick, MA, USA). Example maps are shown in Fig. 1. In brief, regression of the log signal from the 8 PD-weighted echoes was used to calculate a map of R_2^*. The set of echoes for each acquired weighting were then averaged to increase the signal-to-noise ratio (Helms and Dechent, 2009). The 3 resulting volumes were used to calculate MT, R1, and PD* maps as described in Helms et al., 2008a, 2008b; Weiskopf et al., 2013. To maximize the accuracy of the R1 map, inhomogeneity in the flip angle was corrected by mapping the B_1^+ transmit field according to the procedure detailed in Lutti et al. (2012) and the intrinsically imperfect spoiling characteristics were corrected using the approach described by Preibisch and Deichmann (2009).