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Quantitative MRI provides markers of intra-, inter-regional, and age-related differences in young adult cortical microstructure

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ABSTRACT

Measuring the structural composition of the cortex is critical to understanding typical development, yet few investigations in humans have charted markers *in vivo* that are sensitive to tissue microstructural attributes. Here, we used a well-validated quantitative MR protocol to measure four parameters (R_1, MT, R_2*, PD*) that differ in their sensitivity to facets of the tissue microstructural environment (R_1, MT: myelin, macromolecular content; R_2*: myelin, paramagnetic ions, i.e., iron; PD*: free water content). Mapping these parameters across cortical regions in a young adult cohort (18–39 years, N = 93) revealed expected patterns of increased macromolecular content as well as reduced tissue water content in primary and primary adjacent cortical regions. Mapping across cortical depth within regions showed decreased expression of myelin and related processes – but increased tissue water content – when progressing from the grey/white to the grey/pial boundary, in all regions. Charting developmental change in cortical microstructure cross-sectionally, we found that parameters with sensitivity to tissue myelin (R_1 & MT) showed linear increases with age across frontal and parietal cortex (change 0.5–1.0% per year). Overlap of robust age effects for both parameters emerged in left inferior frontal, right parietal and bilateral precentral regions. Our findings afford an improved understanding of ontogeny in early adulthood and offer normative quantitative MR data for inter- and intra-cortical composition, which may be used as benchmarks in further studies.

A core challenge for human neuroscience is the design of robust anatomical imaging methods that are sensitive to inter-regional differences in tissue properties, and to profiles of intra-cortical tissue change from the grey-white border to the pial surface in any one region. The parcellation of human cortex based on cyto- and myeloarchitectonic boundaries has been a major pursuit since the work of Brodmann and Flechsig in the early 20th century (Sereno et al., 2013; Glasser et al., 2016; Turner, 2015; Nieuwenhuys, 2013; Nieuwenhuys et al., 2014; Zilles et al., 2015). However, it is only recently that such questions have been addressed *in-vivo* in humans. This is made possible by the use of magnetic resonance imaging (MRI), which can provide data for morphometry (Ashburner and Friston, 2000; Dale et al., 1999; Fischl et al., 1999a, 1999b) or microstructure (Weiskopf et al., 2015).

The MR signal is sensitive to many important tissue properties, such as iron content, myelin, cell density and water content; however, the contrast-weighted images (T_{1w}, T_{2w}) typically used in MRI reflect a complex mix of these properties that can vary non-linearly across the imaged volume. By comparison, *Quantitative MRI* (Bock et al., 2013; Barazany and Assaf, 2012; Dinse et al., 2013, 2015; Stüber et al., 2014; Marques et al., 2010; for review, see Turner, 2015, 2016; Bazin et al., 2014; Cohen-Adad, 2014; Sereno et al., 2013; Dick et al., 2012) can be used to map specific MRI properties of tissue in order to provide indices

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of microstructure, myelination and related cellular processes (Helms et al., 2008a, 2009; Weiskopf et al., 2013; Lutti et al., 2014) in a time-efficient manner with high spatial specificity. It thus provides the opportunity to acquire a multi-modal, whole-brain view of developmental changes in underlying tissue properties.

In the multi-parameter mapping (MPM) quantitative imaging protocol (Weiskopf et al., 2013; Callaghan et al., 2014b; Helms et al., 2008a, 2008b; Lutti et al., 2014), multiple maps are constructed to probe different tissue attributes. These are 1) the longitudinal relaxation rate, $R_1 = 1/T_1$ (sensitive to myelin, macromolecular content, iron and water); 2) the effective transverse relaxation rate, $R_2^* = 1/T_2^*$ (sensitive to susceptibility effects due to paramagnetic ions, most notably iron, myelin distribution and fibre orientation); 3) Magnetization Transfer (MT; sensitive to macromolecular content and bound water fraction); and 4) effective Proton Density (PD*; sensitive to free water content and residual R_2^* related effects) (Weiskopf et al., 2011; Callaghan et al., 2014a, 2014b; Lutti et al., 2014; Stüber et al., 2014; Fukunaga et al., 2010; Cohen-Adad et al., 2012; Mangeat et al., 2015; Lee et al., 2010, 2011; Bender and Klose, 2010; Denk et al., 2011). These methods allow quantitative measurement of inter- and intra-regional differences in tissue properties (e.g., Cohen-Adad et al., 2012, 2014; Govindarajan et al., 2015; Dinse et al., 2015; Marques et al., 2017) including age-related changes in subcortical fibre tract myelination (Yeatman et al., 2014), pathological changes in neurotrauma (Freund et al., 2013), maturation effects (Whitaker et al., 2016), and age-related tissue de-myelination (Callaghan et al., 2014a), whilst affording the means to do so in relation to functional ability (e.g., Gomez et al., 2017). Such mapping methods have also been used to identify the heavily-myelinated boundaries of visual (Sereno et al., 2013; but see Abdollahi et al., 2014), primary auditory (Dick et al., 2012; de Martino et al., 2015; Sigalovsky et al., 2006), and somatomotor areas (Carey et al., 2017), when relating these regions to function.

Charting the normal development and aging of human cortical tissue is a fundamental goal of neurobiology, and is also critical for accurately characterizing atypical development, individual differences, and short- and long-term plasticity. Development is reported to follow a posterior-to-anterior gradient with primary areas maturing earliest in life and association areas, which mediate higher-order functions, developing later (Gogtay et al., 2004; for review of processes, see Marsh et al., 2008). At earlier points in development through adolescence, there is evidence to suggest that deviation from typical trajectories may increase vulnerability to psychiatric disorders (Thompson et al., 2001; Greenstein et al., 2006; Sowell et al., 2003; Shaw et al., 2007) whereas in later life, such deviation may be indicative of neurodegenerative decline, for which age is often the greatest predictor (Barkhof et al., 2009; Bartzokis, 2004, 2011; Frisoni et al., 2010). A cornerstone in the development of mature cortex is the emergence of myelinated fibres within the cortical sheet (Flechsig, 1920; Yakovlev and Lecours, 1967; Deoni et al., 2015). Though the exact trajectories are unclear, the rate at which change occurs – and the age at which development stabilizes – are thought to be region-specific (e.g. Yeatman et al., 2014; Whitaker et al., 2016) and to interact with functional organization (e.g. Yeatman et al., 2012; Gomez et al., 2017).

To date, few quantitative imaging studies have explored developmental changes in tissue composition across cortex from late adolescence to the mid-thirties. This is a crucial age range to characterize, not least because it is the 'sample of choice' for the vast majority of structural and functional MRI studies. Here, we used the multi-parameter mapping (MPM) protocol (Weiskopf et al., 2013; Callaghan et al., 2014a, 2014b; Helms et al., 2008a, 2008b) to explore potential parameter-specific (R_1, MT, PD*, R_2^*) variation in tissue over the depth of the cortical sheet, and across a range of cortical regions. Further, we charted age-related differences in cortical microarchitecture across early adulthood. We mapped a set of normative, cortical-depth-specific regional MPM values for young adults that can be used as reference values for future studies. Moreover, we found considerable, region-specific age-related changes in parameters related to the degree of tissue myelin content and myelin-related processes.

Materials and methods

Participants

Participants were 93 right-handed healthy adults (mean age ± SD: 23.6 ± 4.3; range: 18–39; 57 female, 36 male). The study received approval from the local ethics committee. All scanning took place at the Wellcome Trust Centre for Neuroimaging (WTCN), London.

Participants were sampled over approximately 24 months. Thirty-four participants were recruited as part of a study of musicianship and consisted of expert violinists ($n = 18$; mean age ± SD: 22.8 ± 2.8; 13 female, 5 male) and closely matched non-musicians ($n = 16$; mean age ± SD: 23.3 ± 3.1; 12 female, 4 male). All had completed or were enrolled in a university degree, and were recruited from the University of London, music conservatories in London, and local participant pools. We analyzed data for effects of violin expertise and will report these findings in a subsequent report. In brief, effects of violin expertise in cortex were modest and emerged only in ROI analyses of primary auditory cortex, where we found limited evidence of significant age-related effects in the present study.

The remaining participants ($n = 59$; mean age ± SD: 23.9 ± 4.9; 32 female, 27 male) were sampled from the general population through local participant pools. These subjects took part in three experiments: one exploring the potential association between auditory perceptual abilities, musicianship, tonotopic organization and structural properties of the auditory cortex (data not reported here), one investigating the relationship of trait empathy and brain microstructure (Allen, Frank, et al., 2017), and a third investigating metacognition and MPM assays (Allen et al., 2017).

There was no significant difference in age between genders across the full cohort ($z = 0.85$, $p > 0.4$), nor any significant effects of gender on MPMs in any models (all $p > 0.3$).

Data acquisition

The multi-parameter mapping protocol data (Weiskopf et al., 2013; Lutti et al., 2010, 2012) were acquired at the WTCN using a 3T whole-body Tim Trio system (Siemens Healthcare) with radiofrequency body coil for transmission and a 32-channel head coil for signal reception. The MPM protocol consisted of three differently weighted 3D multi-echo FLASH acquisitions acquired with 800 μm isotropic resolution. Volumes were acquired with magnetization transfer (MT_w), T_1-(T_{1w}), and proton density (PD_w) weighting. The MT weighting was achieved through application of a Gaussian RF pulse (4 ms duration, 220° nominal flip angle) applied 2 kHz off-resonance prior to non-selective excitation.

Two further scans were collected to estimate participant-specific inhomogeneities in the RF transmit field (B_1^+) using a 3D EPI acquisition of spin-echo (SE) and stimulated echo (STE) images as described in Lutti et al. (2010) (slice thickness: 4 mm; matrix size: 64 × 48 x 48; field-of-view: 256 × 192 × 192 mm^3; bandwidth: 2298 Hz/pixel; SE/STE acquisition time post-excitation: 39.38 ms/72.62 ms; TR: 500 ms). In addition, a map of the B_0 field was acquired and used to correct the B_1^+ map for off-resonance effects (Lutti et al., 2010; see also Weiskopf et al., 2006) (voxel size: 3 × 3 × 2 mm^3; slice thickness: 4 mm; field-of-view: 192 × 192 mm^2; 64 slices, 1 mm gap; bandwidth: 260 Hz/pixel; TE1 10 ms, TE2 12.46 ms; TR: 1020 ms; flip angle: 90°).

The sequence settings of the MPM protocol were modified following collection of data for the musicianship sample (cohort 1, $n = 34$), reflecting the on-going development of the MPM sequences at the WTCN. Cohort-specific details follow.