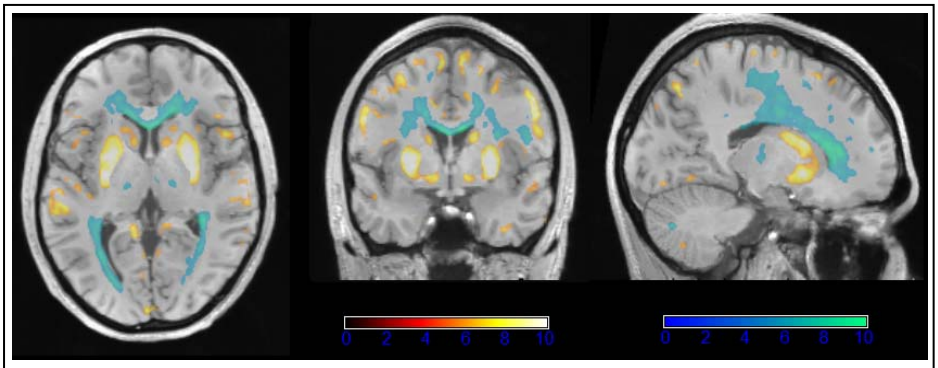
Aging of the central nervous system: a voxel-based quantification (VBQ) study of 100 volunteers

Martina F. Callaghan[1], Patrick Freund[1,2], Bogdan Draganski[3], Marinella Cappelletti[1], Thomas Fitzgerald[1], Peter Smittenaar[1], Antoine Lutti[1], and Nikolaus Weiskopf[1]
[1]Wellcome Trust Centre for Neuroimaging, UCL Institute of Neurology, London, United Kingdom, [2]Spinal Cord Injury Center Balgrist, University Hospital Zurich, Zurich, Switzerland, [3]LREN, Department des Neurosciences Cliniques, CHUV, Universite de Lausanne, Lausanne, Switzerland

Target Audience: Those interested in multivariate analysis of tissue microstructure and the alterations that occur during aging.

Purpose: Quantitative magnetic resonance (MR) parameters are a direct reflection of intrinsic tissue microstructure. Microstructural changes that occur during aging are known to be reflected by quantitative changes in these MR parameters[1]. Here regional changes in brain and spinal cord microstructure that accompany healthy aging are assessed by analysing quantitative maps of longitudinal relaxation rate (R1), transverse relaxation rate (R2*) and magnetisation transfer (MT).



SPMs (p<0.05 FWE corrected) illustrating significant positive correlation between R2* and age (red/white) and significant negative correlation between MT and age (blue/green). The respective t-scores are indicated by the colour bars.

Methods: 100 healthy subjects (42 male, age range 18-74yrs, mean 36yrs, std. dev. 18yrs) were scanned on a 3T whole body system (TIM Trio, Siemens). Multi-echo 3D fast low angle shot (FLASH) datasets with 1mm isotropic resolution were acquired each with predominantly T1, PD or MT weighting[2,3] along with calibration sequences to correct for B1 inhomogeneities[4]. The quantitative maps were derived from this data using bespoke MATLAB tools (The Mathworks, USA). The MT maps were segmented into grey and white matter using SPM8 (Wellcome Trust Centre for Neuroimaging, London). To maximise precision of inter-subject alignment and to preserve the quantitative values in the maps, spatial normalisation was performed using the DARTEL algorithm as described in Draganski *et. al*[1] with an isotropic smoothing kernel of 3mm full width at half maximum. Voxel-based statistical analysis was carried out using a whole-brain approach with covariates of age, gender, total intra-cranial volume and measures of cross-sectional cord area, mean spinal cord MT and R_2* defined on 15 axial slices superior from C2.

Results: Significant positive correlation between R_2* and age was seen in the putamen, pallidum and caudate nucleus as well as in regions of the cortex including motor, somatosensory and visual areas. Significant negative correlation between MT and age was seen in the corpus callosum, along the optic radiations and in widespread white matter regions. Significant negative correlation between R1 and age was seen in the genu of the corpus callosum and the optic radiations. No correlation was seen between spinal cord metrics and the parameter maps. Linear regression between spinal cord area and age was not significant in an ANOVA test.

Discussion: The observed reduction in MT and R1 and increase in R2* with age are in line with previous histological and imaging studies. MT and R1 are sensitive to myelination and reflect the reduction of white matter myelination that occurs as part of the natural aging process. R2* is sensitive to increases in non-heme iron content. The regional changes identified reflect the increases in iron content known to occur on a microstructural level during aging.

Conclusion: Spatially localised changes in iron deposition and myelination that have been associated with the healthy aging process through post mortem studies are made visible *in vivo*, on a regional basis, through voxel based quantification (VBQ). The sensitivity required to detect such microstructural changes arises because of the robust quantitative approach taken and the high statistical power derived from having such a large cohort of 100 volunteers. This quantitative approach will be of great benefit for future studies, not only for gaining insight into the changes that occur during healthy aging but also for establishing normative MR parameter values across ages and for monitoring the evolution and underlying causes of pathological conditions.

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References: 1. Draganski, B. *et al. NeuroImage* **55**, 1423–34 (2011); 2. Helms, G., Dathe, H. & Dechent, P. *MRM* **59**, 667–72 (2008); 3. Helms, G. & Dechent, P. *JMRI* **29**, 198–204 (2009). 4. Lutti, A. *et al. PloS one* **7**, e32379 (2012).