Whole-brain in-vivo measurements of the axonal g-ratio in a group of 19 healthy volunteers

Siawoosh Mohammadi[1], Daniel Carey[2], Fred Dick[3], Joern Diedrichsen[4], Martina F. Callaghan[5], Marty Sereno[2], Marco Reisert[6], and Nikolaus Weiskopf[5]
[1]*Department of Systems Neuroscience, University Medical Center Hamburg-Eppendorf, Hamburg, Hamburg, Germany,* [2]*Birkbeck/UCL Centre for NeuroImaging, London, London, United Kingdom,* [3]*Birkbeck/UCL Centre for NeuroImaging, London, United Kingdom,* [4]*UCL Institute of Cognitive Neurology, London, United Kingdom,* [5]*Wellcome Trust Centre for Neuroimaging, UCL Institute of Neurology, London, United Kingdom,* [6]*University of Freiburg Medical Center, Freiburg, Germany*

TARGET AUDIENCE: Researchers studying brain microstructure and relationship between axon and myelin concentration.

PURPOSE: Understanding the normal and diseased human brain crucially depends on reliable knowledge of its anatomical microstructure as it evolves during life. During the last decade quantitative MRI (qMRI) has facilitated the observation of microstructural changes in-vivo [1]. Although conventional qMRI techniques such as diffusion tensor imaging are sensitive to microstructural changes, they are unspecific to the underlying tissue compartments, e.g. they can detect microstructural changes in multiple sclerosis but not distinguish demyelination from remyelination [2]. Thus, they are less suitable as MRI-based biomarkers. One approach to improving the specificity relies on advanced biophysical models that relate the MRI signal to the underlying microstructural characteristics. An important microstructural property is the g-ratio of fiber pathways [3], i.e. the ratio between inner and outer fiber diameter, since it has been shown that the g-ratio is related to conductance velocity, can change due to functional stimulation [4] and more specifically reflects the integrity of nerve fibers than standard qMRI [5]. Yet, the g-ratio distribution in humans has been investigated only in few healthy volunteers and there is little known about its variation within the population. We determine in-vivo the spatial distribution of the g-ratio across the whole brain within a group of healthy volunteers and compare it to ex-vivo histology literature values [5].

METHODS: 19 healthy volunteers were scanned at 3T using an 800µm multi-parameter mapping (MPM) protocol [6,7] and a 2.3 mm standard high-angular-resolution diffusion imaging (HARDI) protocol [8]. The calculation of the aggregate g-ratio was based on Stikov et al.'s [3] model that relates the g-ratio to the ratio of myelin (MVF, derived from MPM data) and fiber (FVF, derived from HARDI data) volume fraction within a given volume. As compared to recent approaches [3,5] we introduced three innovations ensuring a faster and more robust acquisition of the g-ratio maps: (a) *MVF* was estimated by a magnetization transfer (MT) map from the MPM protocol, which uses multi-echo Fast Low-Angle Shot (FLASH) acquisitions with high SNR and image quality [6,9,10], (b) *FVF* was calculated using the Tensor Fiber Density (TFD) of Reisert et al. [11], which unlike higher-order diffusion models can be directly estimated from a comparatively small standard HARDI dataset, (c) we corrected for susceptibility-related distortions in the HARDI data to improve alignment between HARDI and MT data using the HySCO-ACID toolbox [12]. The resulting expression for the g-ratio was: $g = \sqrt{1 - MVF/FVF} = \sqrt{1 - \alpha MT/TFD}$, where the same $\alpha = 0.04$ was used for all subjects and it was determined by normalizing to a literature value of $g = 0.8$ for the splenium. To transform individual g-ratio maps into a common group space we used DARTEL in SPM8 [13,14]. We calculated the voxel-wise mean and standard deviation of the g-ratio across volunteers. The group mean in-vivo g-ratio was compared to ex-vivo histology[5] measures of the g-ratio.

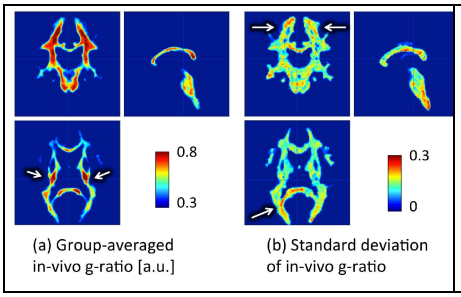

Fig. 1: Group g-ratio maps. Mean (a) and standard deviation (b). (a) The g-ratio is highest in the genu, midbody and splenium of the corpus callosum and within the cortico-spinal tracts (arrows). (b) Inter-individual variation is particularly high in the left part of the splenium and cortico-spinal tracts near the cortex (arrows).

RESULTS AND DISCUSSION: The in-vivo g-ratio across a group of healthy volunteers followed the observations from ex-vivo histology of the corpus callosum [5]: it was highest in the genu, midbody and splenium of the corpus callosum (Fig. 2). Furthermore, the g-ratio was highest along the cortico-spinal tracts (Fig. 1a, arrows), which is populated by axons that have the largest diameter [15] within the whole brain in keeping with the general histological finding of larger fibers having larger g-ratio. The inter-individual variation of the g-ratio was highest in the splenium and the cortico-spinal tracts towards the motor cortex (Fig. 1b, arrows). We note potential limitations of MRI-based g-ratio measures: (a) there are different approaches to estimate the FVF [5,11] and MVF [3] and there is no conclusive answer to which method works best, (b) the assumption that it represents the aggregate g-ratio might be violated in some regions because the percentage of unmyelinated fibers is not constant over the brain [16], (c) our comparison with ex-vivo histology is of a qualitative nature only, because the ex-vivo g-ratio was measured in a macaque [5].

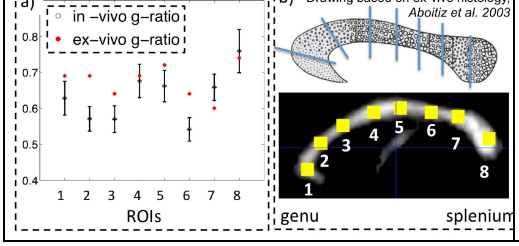

Fig. 2: (a) Comparison between in-vivo (black) and ex-vivo (red) g-ratio measures in the corpus callosum. (b) Following the dissection of the corpus callosum by Stikov et al. [4] for ex-vivo histology (top row), we calculated the standard deviation and the mean of the g-ratio in 8 different region of interests (ROI, bottom row). Our g-ratio measure followed the trend of the ex-vivo measurements (a).

CONCLUSIONS: This is the first study that demonstrates inter-individual variation of the in-vivo g-ratio in white matter using standard acquisition methods. We found qualitative agreement between the in-vivo and ex-vivo g-ratio. The in-vivo g-ratio measure holds promise as a biomarker in neuroimaging, clinical research and diagnosis.

Acknowledgements: This work was supported by the Wellcome Trust and the European Research Council (ERC grant agreement n° 616905). SM was supported by the Deutsche Forschungsgemeinschaft (DFG, MO 2397/1-1). **References**: 1.Zatorre, R.J. *et al. Nat. Neurosci.* **15**, 528 (2012); 2.Barkhof, F. *et al. Nat. Rev. Neurol.* **5**, 256 (2009); 3.Stikov, N. *et al. NeuroImage* **54**, 1112 (2011); 4.Gibson, E.M. *et al. Science* **344**, 1252304 (2014); 5.Stikov, N. *et al. ISMRM 22 P 2249* (2014); 6.Weiskopf, N. *et al. Front. Brain Imaging Methods* **7:**, 95 (2013); 7.Dick, F. *et al. J. Neurosci. Off. J. Soc. Neurosci.* **32**, 16095 (2012); 8.Mohammadi, S. *et al. Magn. Reson. Med.* **70**, 358 (2013); 9.Lutti, A. *et al. PloS One* **7**, e32379 (2012);10.Weiskopf, N. *et al. Brain Imaging Methods* **8**, 278 (2014); 11.Reisert, M. *et al. NeuroImage* **77**, 166 (2013); 12.Ruthotto, L. *et al. Bildverarb. Für Med. 2013* 344 (2013); 13.Friston, K.J. *et al.* (Academic Press: London, 2006); 14. Ashburner, J. *NeuroImage* **38**, 95 (2007); 15.Graf von Keyserlingk, D. *et al. Anat. Anz.* **157**, 97 (1984); 16.Lamantia, A.S. *et al. J. Comp. Neurol.* **291**, 520 (1990).