A gradient in cortical T2* relaxation decay changes at 7 Tesla MRI in patients with multiple sclerosis

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Target Audience. Neurologists, radiologists, and neuroscientists interested in developing methods for better understanding and assessing in vivo cortical pathology in multiple sclerosis.

Purpose. Studies at post-mortem demonstrated that subpial demyelination is frequent in multiple sclerosis (MS) and is closely associated with disease progression [1]. Subpial lesions pathogenesis in MS, however, remains uncertain partly due to the limited sensitivity of currently available imaging methods. The ex vivo observation that there is a gradient of demyelination through the cortical laminae, with the most dramatic changes seen within the iuxtameningeal cortical layers, supports the hypothesis that cortical degeneration in MS is the consequence of a pathogenic process driven from the pial surface [2]. New pathological data suggest that cortical demyelination likely starts very early in the disease course, independently from white matter (WM) lesions [3]. We previuosly demonstrated that the combination of T_2* relaxation decay at 7 T MRI with a surface-based laminar analysis allows for selective sampling of T_2* at different depths from pial surface, across the whole cortex (**Fig. 1**) [4]. Here, we sought to evaluate whether a laminar analysis of cortical T_2* could demonstrate in vivo a gradient in the expression of MS cortical pathology, until now reported only at post-mortem in chronic MS.

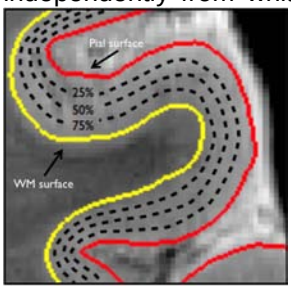

Fig. 1. Detail of the cortex from axial multi-echo 7 T T2* image. Dashed lines represent the surfaces that can be used for sampling T_2* at 25%, 50% and 75% depth from pial surface.

Methods. We recruited 27 patients (mean, range age=42.8, 26-61 years) according to three disease phenotypic categories: 1) 7 subjects with clinically isolated syndrome (CIS)/early relapsing-remitting (RR) MS with disease duration ≤3 years; 2) 14 subjects with RRMS and disease duration ≥ 4 years; 3) 6 secondary progressive (SP) MS patients. Fourteen age-matched healthy volunteers were included as controls (mean, range age=38, 30-56 years). Subjects were scanned at 3 T and 7 T (Siemens Medical Solutions) using a 32-channel coil. T_2* was derived from 7 T multi-echo FLASH-T_2* spoiled gradient-echo images (TR=2020 ms, TE=6.34+3.2n [n=1..12], resolution=0.33x0.33x1 mm^3). Data were first corrected for gradient non-linearity, then T_2* was calculated voxel-wise using a Levenberg–Marquardt non-linear regression model as previously detailed [4]. Each individual T_2* map was registered to the cortical surface generated from 3 T data by Freesurfer using a boundary-based registration technique [5]. T_2* was then sampled along the cortex at 25%, 50%, and 75% depth from the pial surface and smoothed using a Gaussian FWHM of 3 mm. A general linear model (GLM) was run on a vertex-by-vertex basis to assess laminar subpial T_2* differences between patients' groups (CIS/early RRMS; RRMS; SPMS) and age-matched controls across the whole cortex.

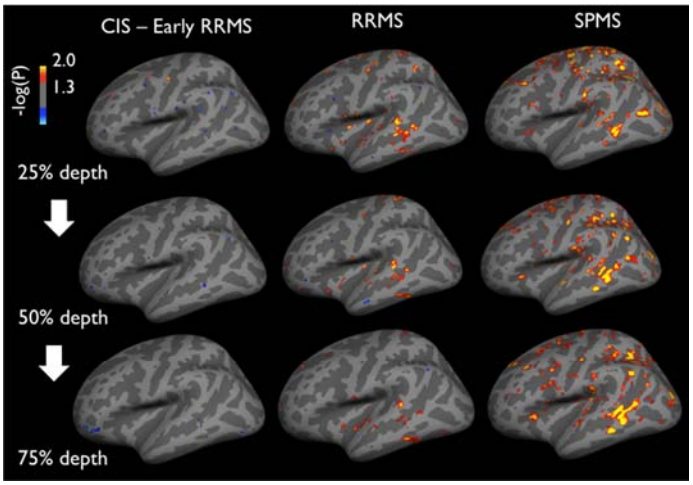

Fig. 2. Overlay of the GLM significance maps on the average pial surface of the left lateral hemisphere for (**left**) CIS and early RRMS, (**middle**) late RRMS, and (**right**) SPMS patients versus age-matched controls. In early disease significant increases in T_2* occurred at the most superficial cortical layers (25% depth from pia). A similar gradient in the increase of subpial T_2* was seen in late RRMS. SPMS showed diffuse subpial T_2* changes at all depths.

Results. The GLM analysis disclosed significant differences in cortical T_2* between controls and patients (**Fig. 2**). Overall, early disease patients showed focal areas of increased T_2* at 25% and 50% but not at 75% depth from pial surface, with changes being greater at 25% than at 50% depth, and located in the middle frontal, sensorimotor and cingulate cortex. Late RRMS patients showed a gradient in the increase of subpial T_2* with the most evident increases relative to controls seen at 25% depth, followed by 50% and 75% depth. In this group of patients areas of T_2* increase also involved the orbitofrontal cortex, insula, temporal and parietal cortex. In SPMS there were diffuse subpial T_2* changes across the cortical mantle, at all depths.

Discussion. In early disease cortical changes are focal and mainly confined to the iuxtameningeal cortical layers. As MS progresses cortical changes involve deeper cortical laminae, and extend across multiple cortical areas.

Conclusion. We demonstrate *in vivo* a gradient in the expression of cortical MS pathology. Future longitudinal studies are needed to confirm these preliminary observations.

References. [1] Peterson, *Ann Neurol* 2001. [2] Magliozzi, *Ann Neurol* 2011.[3] Lucchinetti, *New Engl J Med* 2011. [4] Cohen-Adad, *Neuroimage* 2012. [5] Greve, *Neuroimage* 2010. This work was supported by NMSS 4281-RG-A1; FG 1892A1/1, NIH P41-RR14075.