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 previously demonstrated that the combination of T2* relaxation decay at 7 T MRI with a surface-based laminar analysis allows for selective sampling of T2* at different depths from pial surface, across the whole cortex (Fig. 1) [4]. Here, we sought to evaluate whether a laminar analysis of cortical T2* could demonstrate in vivo a gradient in the expression of MS cortical pathology, until now reported only at post-mortem in chronic MS.

**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. T2* was derived from 7 T multi-echo FLASH-T2* spoiled gradient-echo images (TR=2020 ms, TE=6.34+3.2n [n=1…12], resolution=0.33x0.33x1 mm³). Data were first corrected for gradient non-linearity, then T2* was calculated voxel-wise using a Levenberg–Marquardt non-linear regression model as previously detailed [4]. Each individual T2* map was registered to the cortical surface generated from 3 T data by Freesurfer using a boundary-based registration technique [5]. T2* 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 T2* differences between patients’ groups (CIS/early RRMS; RRMS; SPMS) and age-matched controls across the whole cortex.

**Results.** The GLM analysis disclosed significant differences in cortical T2* between controls and patients (Fig. 2). Overall, early disease patients showed focal areas of increased T2* 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 T2* 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 T2* increase also involved the orbitofrontal cortex, insula, temporal and parietal cortex. In SPMS there were diffuse subpial T2* 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.