Cortical Oxygen Extraction as a Marker of Disease Stage and Function in Multiple Sclerosis: a Quantitative Study using 7 Tesla MRI Susceptibility.

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Introduction. Cortical damage is thought to play a major role in determining progressive physical and cognitive disability in multiple sclerosis (MS). There is pathological evidence that the type and location of lesions arising in the cortex are closely related to the size and territory of involved cortical veins, and histological data suggest that the initial inflammatory process in MS originates around small veins [1,2]. Characterization of venous function, including venous oxygen extraction fraction (OEF) in the cortex, would provide new insights into metabolic changes associated with lesion formation in MS. Recently, using a T2-based MRI method, Ge et al. found a decrease in absolute OEF in the sagittal sinus of patients with relapsing remitting MS (RRMS) relative to healthy controls [3].

This study directly quantified OEF in individual cortical veins from patients at different stages of MS disease using a distinct MR approach based on magnetic susceptibility. The study was performed at ultra-high field (7T) to take advantage of the improved signal-to-noise ratio for sub-millimeter resolution in phase images, allowing measurements of OEF across multiple cortical regions. Quantitative cortical OEF was evaluated against 1) measures of tissue damage in the cortex, deep gray matter (GM), and white matter (WM); and 2) neuropsychological (NP) tests to investigate whether OEF is a marker of cognitive performance in MS.

Methods. _Subjects_. We recruited patients with clinically isolated syndrome (CIS, n=6), RRMS (n=11), and secondary-progressive (SP) MS (n=7), and age-matched controls (n=9). Subjects were scanned on a 7T Siemens MRI with an in-house 32-channel coil. Patients also underwent neuropsychological (NP) testing and z-scores were computed for processing speed, executive function, and learning-recall ability. _MRI Acquisition_. For susceptibility measurements, axial 3D flow-compensated FLASH images were acquired with magnitude and phase (TR/TE=26/ 6,10ms; resolution=0.33x0.33x1.0mm^3; matrix=576x504x64; BW=130Hz). Additional 2D FLASH-T2*-weighted spoiled gradient-echo images were acquired for characterization of WM lesion volume (LV), deep GM LV, and cortical lesion counts (LCs) [4]. _OEF quantification_. Phase images were high-pass filtered (96x96 Hanning) to remove background fields [5]. Long cortical pial veins parallel to the main field (B$_0$), as in Fig 1, were manually identified and the field shift between the vein and surrounding tissue, $\Delta B_{vein\text{-}tissue}$, was calculated using phase from both TEs [6]. Using MR susceptometry, local OEF for each parallel vessel was determined: $\Delta B_{vein\text{-}tissue} = 1/6\cdot4\pi\ \Delta\chi_{do}\cdot Hct\ \cdot \textbf{OEF}\ \cdot(3\cos^2\theta-1)\cdot B_0$, where vessel tilt θ=0, $\Delta\chi_{do}$=0.18ppm, and hematocrit Hct=0.4 [7,8]. In each subject, OEF was averaged from 5-6 veins across the cortex.

Results. Patients with late disease (>3 years duration) exhibited decreased cortical OEF relative to controls (~6.2%, p=0.024) using a one-way ANOVA (Fig 2). Patients with early disease (<3 years duration) had a 3.0% absolute reduction in OEF. Across all patients, OEF negatively correlated with disease duration (p=0.02) and WM LV (p<0.01). Eleven out of 24 patients failed in at least one cognitive test; however only six (25%) were strictly cognitively impaired. Impaired patients had higher WM lesion volume (p<0.001), Type I (p<0.01), and Type III/IV (p=0.03) cortical lesions than unimpaired patients (two-sample t-test), while differences in OEF were less evident (p=0.07). Across all patients, however, decreased OEF was strongly associated with reduced cognitive performance (Fig 3). Cortical OEF was found to be the main independent predictor of processing speed (p=0.03, forward stepwise linear regression).

Discussion. This study represents the first quantification of OEF in the cortex of patients with different MS phenotypes. We observed a trend of decreased cortical OEF, present even in the early disease stages, which progresses with disease duration and disability. Our work also characterizes cortical OEF as a sensitive marker of cognitive function in MS, particularly of processing speed. Interestingly, our results derive from a patient sample with relatively preserved cognitive function. We hypothesize that our measures may be more sensitive to earlier pathological stages of MS in which metabolic dysfunction likely plays a greater role than structural changes on clinical status. This work implicates metabolic deficiency early in the development of cognitive dysfunction in MS and highlights OEF as a useful new metric of cortical pathology.

References. [1] Adams, _J Neurol Sci_ 1989. [2] Kidd, _Brain_ 1999. [3] Ge, _Proc ISMRM_ 2011. [4] Mainero, _Neurology_ 2009. [5] Wang _J Magn Reson Imag_ 2000. [6] Fan _Magn Reson Med_ 2011. [7] Haacke _Human Brain Mapp_ 1997. [8] Weisskoff _Magn Reson Med_ 1992. **We thank Drs. Julien Cohen-Adad, Lawrence Wald, and Boris Keil.**
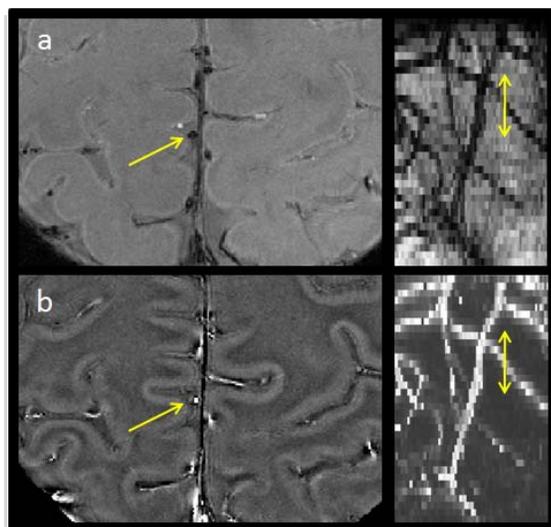
Fig 1. (a) Magnitude and **(b)** phase highlighting an individual cortical vessel (arrows) from a patient with CIS in axial (left) and sagittal (right) views.
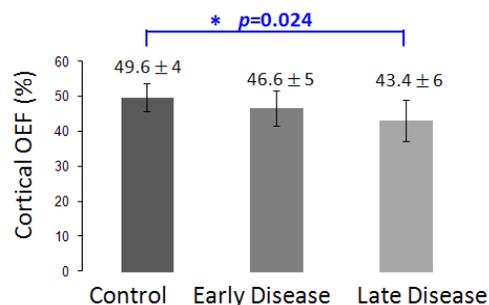

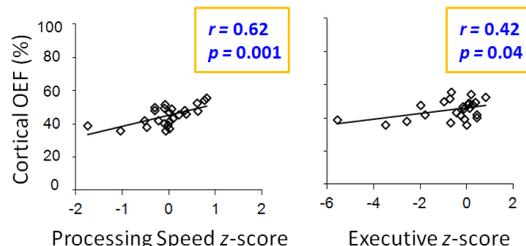**Fig 2.** Mean cortical OEF in patients with late disease was significantly lower than control subjects.

Fig 3. Pearson correlations between cortical OEF and cognitive z-scores across all patients.