Iron as a source of laminar contrast in MRI of human cerebral cortex

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Introduction: The possibility that the cellular microstructure of the brain might reveal its functional architecture has long intrigued neuroscientists[1,2]. For example, grey matter cell density and myelin content both vary across the cortical depth and this variation can sometimes be revealed by in-vivo MRI based on spin density and T_1 contrast. We recently demonstrated that magnetic susceptibility also varies across cortical layers and that the associated shifts in magnetic resonance frequency, as determined from the phase of the T_2*-weighted MRI signal, can lead to superb laminar contrast in a number of brain regions[3], most notably the line of Gennari (layer 4b) in the primary visual cortex. Here, we attempted to assess the contribution of one the major postulated susceptibility sources, iron, to the observed frequency shifts in this region (Fig. 1a,b).

Methods: In order to determine the contribution of iron to intra-cortical contrast, we used the iron extraction method as described previously[4]. This involved high-resolution MRI scanning of formalin-fixed brain tissue samples prior to and after extraction. Iron extraction was performed over 7 days using a solution of desferrioxamine and sodium dithionite[4]. The tissues were derived from patients (n=3) with a history free of neurological diseases. The scans were performed on a 7 T GE whole-body MRI scanner, using a dedicated 4-channel detector, a dual-echo gradient recalled echo acquisition (TE=15 ms, TE=30 ms and a resolution of 50x50x500 μm). For comparison, in-vivo MRI data was obtained in 6 normal volunteers at 220x220x500 μm resolution in a scan time of 12 minutes[3]. Data analysis included the calculation of phase, R_2*, and magnitude images. Perls' iron staining was performed in some tissue sections using DAB intensification[5] and some samples were scanned at 11.7 T at 12.5 μm isotropic resolution.

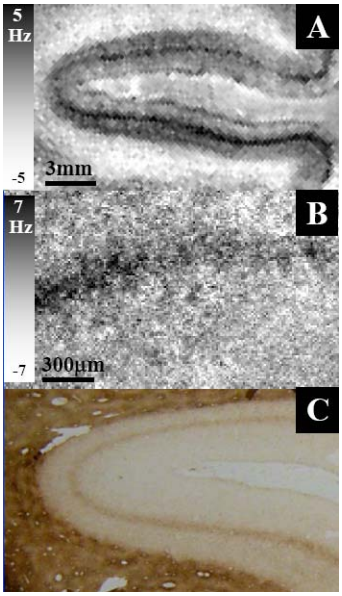

Figure 1: Frequency shifts observed in-vivo (A, 7 T) and in-vitro (B, 11.7 T) in human V1. A Perls' iron stain of V1 is shown in C.

Results: Iron histology suggested that, in addition to high myelination in the line of Gennari, iron is also increased in this region (Fig. 1c). All in-vivo and pre-extraction in vitro MRI phase data scans showed a characteristic darkening (negative frequency shift) in central regions of the primary visual cortex (Figs. 1 and 2). Comparison of pre- and post extraction MRI data showed that the iron extraction resulted in an overall decrease in frequency and R_2* in both white matter (WM) and grey matter (GM). On average pre/post extraction R_2* values were 45/34, 31/17, and 20/15 s^{-1} for WM, GM in deep layers, and GM in superficial layers respectively. In addition, a complete elimination of the central darkening effect in the phase data was observed (Fig. 2). Moreover, faint evidence of phase reversal was observed in the Gennari line in 2 of the 3 post-extraction samples. The R_2* contrast in this region was reduced but not entirely eliminated.

Discussion: The results are interpreted as follows: 1. Iron varies substantially across cortical layers in V1. 2. The similar appearance of cortex in in-vivo and pre-extraction ex-vivo MRI suggests that iron in hemoglobin is not a major contributor to the contrast; 3. The virtual elimination of cortical phase contrast with iron removal suggests iron as the main contrast source; 4. The slight brightening remaining in the myelin-rich central region of the visual cortex, and the positive frequencies observed in the white matter confirm the hypothesis that myelin causes a frequency shift opposing that of iron[3,6]. This effect is relatively small in the line of Gennari, consistent with its lower myelin content as compared to sub-cortical white matter. 5. While iron and myelin both increase R_2*, they have different (opposing) effects on frequency shifts. Therefore, combined analysis of R_2* and frequency shifts might allow quantitative determination of the relative contribution of iron and myelin to tissue susceptibility changes throughout the human brain.

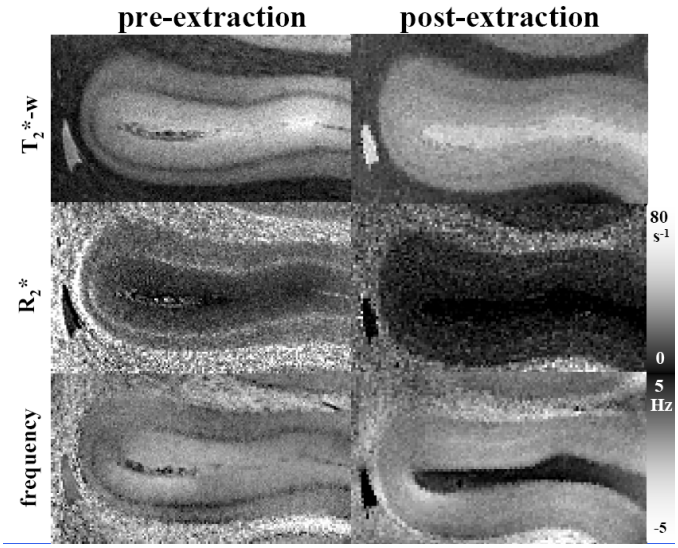

Figure 2: Comparison of pre- and post-extraction contrast in-vitro. Iron extraction virtually eliminates intra-cortical susceptibility shifts. The little contrast remaining in R_2 and frequency images is attributed to myelin.*

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