Investigating the sources of phase contrast: iron oxide nanoparticle study to exclude deoxyhemoglobin as a major source for the gray/white matter phase contrast

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Introduction

Recently, the benefits of image phase for the study of brain anatomy at high field (> 7 T) have been demonstrated [1]. In some brain regions, the improved contrast to noise ratio (over the magnitude images) between and within grey and white matter structures has provided the opportunity to study the laminar structure of the cortex. Several sources such as iron [1,2], myelin [3], deoxy-hemoglobin [4], and macromolecular concentration [5] have been suggested to contribute to the phase contrast. However, the relative contribution of these sources is not well understood. Recently, Marques et al. [6] used an oxygen challenge in rat to demonstrate a relatively small contribution of deoxy-hemoglobin. However, quantitative interpretation of this result was compromised by the limited contrast modulation introduced by this challenge and potential confounds such as associated blood volume changes. Therefore, the result did not fully eliminate deoxy-hemoglobin as a substantial contributor to gray/white matter phase contrast. Here, we administered iron oxide nanoparticles that induce a relatively large increase in vascular susceptibility to further confirm that deoxy-hemoglobin is not a major source for the gray/white matter contrast.

Methods

All scans were performed at a 7 Tesla (Bruker BioSpin) animal system with a 4 channel surface coil. The scan sequence for phase images was a 2D multi-echo GRE sequence with FOV = 2.56 x 2.56 cm^2, resolution = 67 x 67 x 500 μm^3, flip angle = 60º, TR = 1 sec, TE = 8 / 20 / 32 msec, 4 average, and total scan time = 27 min. After coil-combining, phase images were unwrapped and filtered by a 2D Gaussian high-pass filter (FWHM = 26 voxels) to remove large scale phase variations. The frequency images were calculated from a linear fit to the phase change over the three echoes. T_2^* values were also calculated from the multi-echo magnitude data. Scans were performed on an isoflurane anesthetized rat before and after various intravascular administrations of an iron oxide nanoparticle solution (Molday ION, BioPAL). Cumulative doses of 0.5, 0.8, and 3 mg/kg (adjusted for half life) were used. Images were acquired 5 min. after each injection.

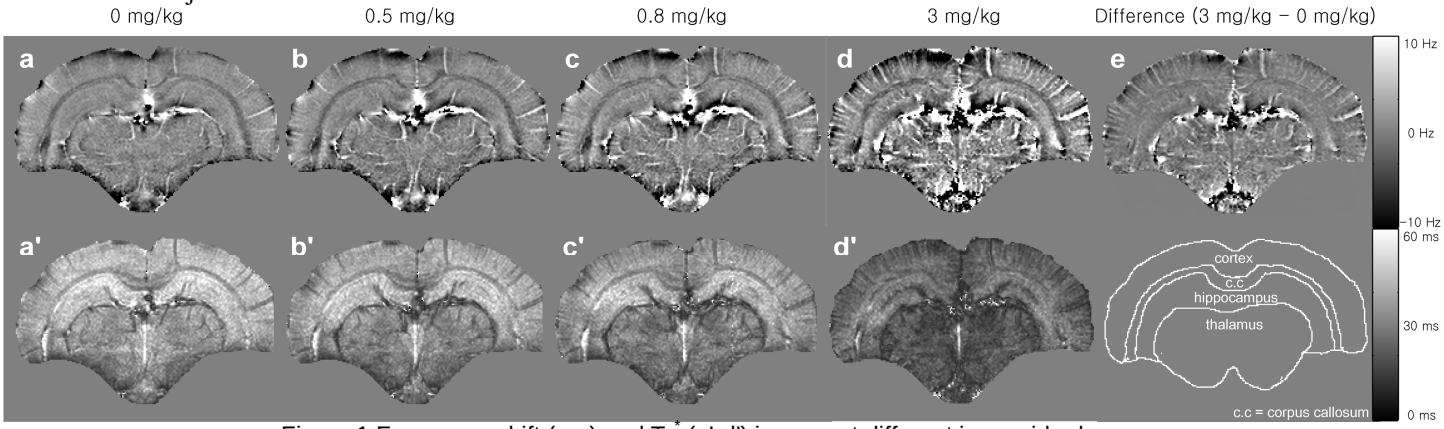

Figure 1 Frequency shift (a-e) and T_2^* (a'-d') images at different iron oxide dosages

Results and Discussion

Figure 1a - d show the frequency images at four different dosages (0 to 3 mg/kg). The positive frequency shifts in the large vessels become more conspicuous with increasing dosages. However, the phase contrast difference between gray (cortex) and white matters (corpus callosum) does not change even with the largest dosage. This effect is better illustrated in the difference images in Fig. 1e where the image was obtained by subtracting no injection result from that of the 3 mg/kg dosage. The gray/white frequency differences measured at 0, 0.5, 0.8 and 3 mg/kg dosages were 1.2 ± 0.4, 1.2 ± 0.5, 1.0 ± 0.5, and 1.2 ± 0.6 Hz respectively. When measured from the first echo phase in large cortical veins, the 3 mg/kg dosage increased the susceptibility in the veins by a factor of 3.7. Based on the higher deoxy-hemoglobin content of large veins (30 to 40 %) versus capillaries (approx. 15 %), the contrast agent induced susceptibility in the capillary bed was estimated to be approximately 6 to 7 times larger than the deoxy-hemoglobin induced susceptibility (both relative to water). The decrease in the T_2^* values (from 44.2 msec at 0 mg/kg to 27.4 msec at 3 mg/kg in gray matter) also confirms the significant effect of the contrast agent. Despite this large increase in susceptibility, the phase contrast between gray and white matter shows virtually no change.

Conclusion

The phase contrast between the gray and white matters is virtually unaffected by the strong increases in intravascular susceptibility induced by the contrast agent. This suggests that the contribution of the much weaker susceptibility of deoxy-hemoglobin does not contribute to the gray/white matter phase contrast.

References [1] Duyn et al, PNAS, 2007, p11796-11801, [2] Haacke et al, MRI, 2005, p1-25 [3] Annese et al, NI, 2004, p15-26, [4] Haacke et al, MRM, 2004, p612-618, [5] Zhong et al, NI, 2008, p1561-1566, [6] J.P. Marques, ISMRM, 2008, p809