Evaluating Feraheme as a potential contrast agent for clinical IRON fMRI

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Introduction:

Feraheme is a carbohydrate-coated iron-oxide nanoparticle that was recently approved by the FDA in the United States for the treatment of iron deficiency anemia in adult patients with chronic kidney disease (http://www.feraheme.com). This agent is a modified version of the USPIO contrast agents that have proved so effective for fMRI in animal models. To test the efficacy of this drug for a potential off-label application to clinical fMRI (e.g., pre-operative brain mapping), we performed experiments in an awake non-human primate (NHP) model using variable doses of feraheme. Results were compared with theoretical calculations in order to extrapolate as a function of dose and field strength.

Methods

Experiments were performed at 3 Tesla in a well-trained NHP using eye fixation reinforced by water reward. Details of this experimental procedure have been published previously [1,2]. Feraheme doses were stepped from 0 mg/kg (BOLD fMRI) to 16.5 mg/kg using a step size of 1.5 mg/kg. At each dose, 3 runs of 5-minute duration were acquired using stimuli of 2, 4, 16, and 32 seconds separated by an inter-stimulus interval of 30 seconds. Stimuli were figures (letters and numbers) embedded in a background noise pattern. Data were analyzed using the general linear model (GLM) with a BOLD impulse response function (IRF) at zero dose and an IRON IRF for all other doses. Data were separated into short (2 sec, 4 sec) and long (16 sec, 32 sec) to investigate the influence of stimulus duration on CNR, which was calculated as the T statistic within the GLM.

Results

Consistent with the 15-hour blood plasma half-life for feraheme in human subjects, no noticeable drift was observed during fMRI experiments in the NHP. Figure 1 shows the temporal response at a dose of 12 mg/kg using a single event type of variable duration to describe the data. Consistent with previous findings, data exhibited a slow response and temporally linearity for stimuli of 4 sec and longer; 2-sec data were underestimated. The IRON IRF well described the data for doses above 3 mg/kg.

Figure 2 shows the experimental CNR for the short and long stimuli using 2 events types within the GLM. CNR is normalized by BOLD CNR at zero dose. Short stimuli exhibited less CNR enhancement as expected. The theoretical calculation [3] ignores differences in the temporal responses of BOLD and IRON signal and so corresponds to the limit of very long stimuli.

Figure 3 employs the experimentally validated theoretical calculations to predict CNR enhancement as a function of dose (mg/kg) at 1.5 and 3 Tesla. The dose range assumes that the FDA-approved dose of 510 mg is injected into subjects with weights between 50 and 100 kg. At 1.5 Tesla, it is expected that feraheme should provide a CNR boost that typically is larger than 5, whereas the expected CNR boost at 1.5 Tesla should be a smaller factor between 2 and 3.

Discussion:

BOLD signal works well for subject-averaged studies, but the limited sensitivity of the technique is a drawback for individualized medicine like pre-operative brain-mapping prior to tumor resection, or potentially even pharmacological studies in clinical populations. This study evaluated the potential efficacy of the FDA-approved dose of feraheme for such fMRI studies. At 3 Tesla, CNR was enhanced by a factor of about 2.5 in the NHP, and the 5-fold increase in CNR at 1.5 Tesla could markedly improve the clinical efficacy and utility of fMRI at this widely available field strength.

References:

1. Vanduffel, W., et al. Neuron, 2001. 32(4): p. 565-577.
2. Leite, F.P., et al. Neuroimage, 2002. 16(2): p. 283-94.
3. Mandeville, J.B., et al. Magn Reson Med, 2004. 52(6): p. 1272-81.

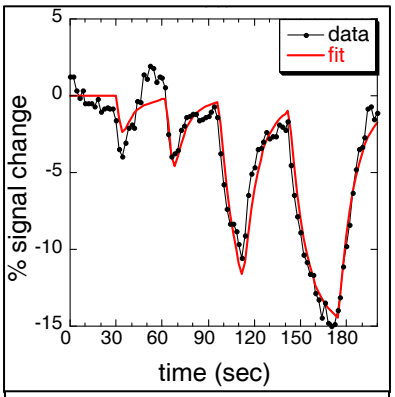

Fig. 1 Temporal response of fMRI signal at a large feraheme dose for 2, 4, 16, and 32 sec stimuli.

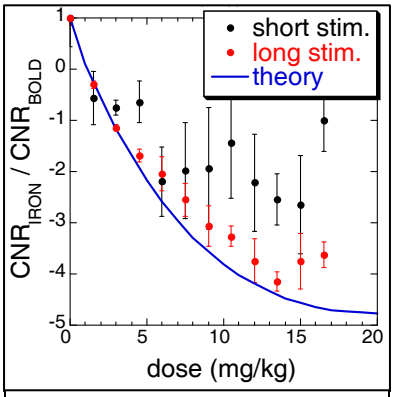

Fig. 2 CNR enhancement versus feraheme iron dose for short (2, 4 sec) and long (16, 32 sec), together with a calculation appropriate for very long stimuli.

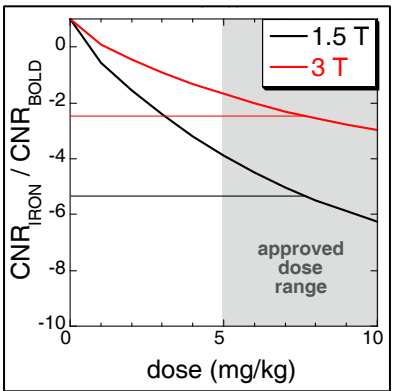

Fig. 3 Predicted boosts in CNR at 1.5 and 3 Tesla using the FDA-approved iron dose.