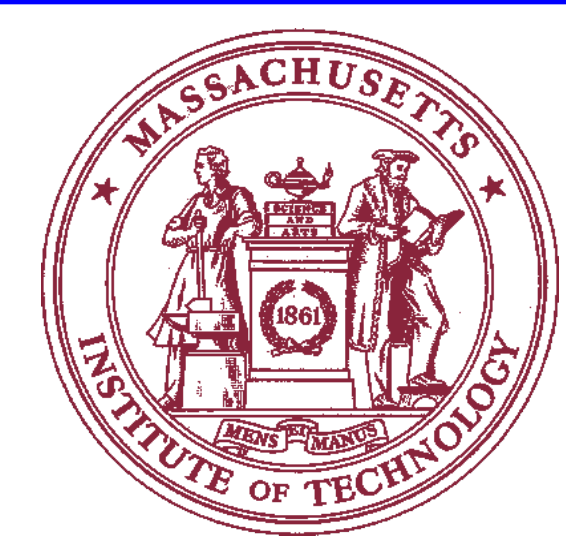




Evaluating Feraheme as a potential contrast agent for clinical IRON fMRI



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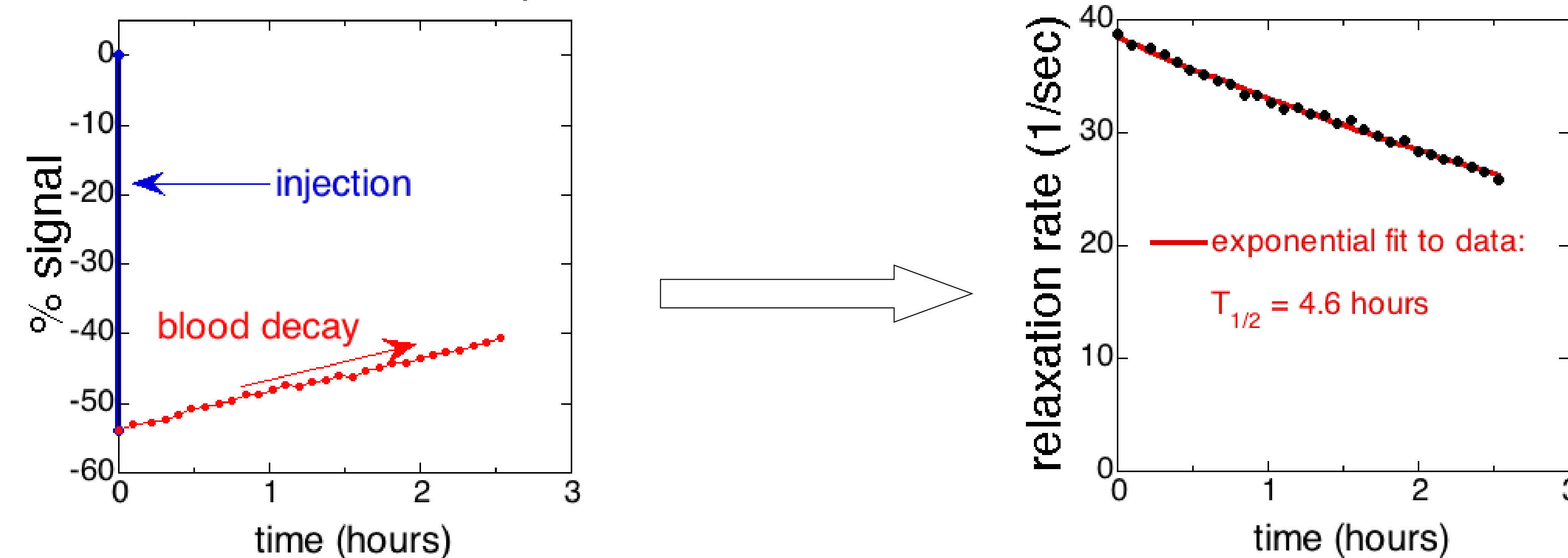


Background

- While BOLD signal is robust in cross-subject studies, low intra-subject BOLD sensitivity is one factor that has limited fMRI clinical applications.
- Iron oxide contrast agents have proven very useful for fMRI in animal models due to the high contrast to noise ratio (CNR) of the method relative to BOLD signal or other fMRI techniques [1-6].
- This technique has never been applied in human subjects due to a lack of approved agents that are suitable for fMRI using the IRON method (IRON = increased relaxation for optimized neuro-imaging)
- Recently, an iron oxide compound (Feraheme) was FDA-approved as an iron supplement at a dose that should be efficacious for fMRI.
- We evaluated this agent using fMRI in awake non-human primates in order to predict CNR for human studies as a function of dose and field.

Results: half life

- Half-life of relaxation rate provides sufficient time for fMRI studies.

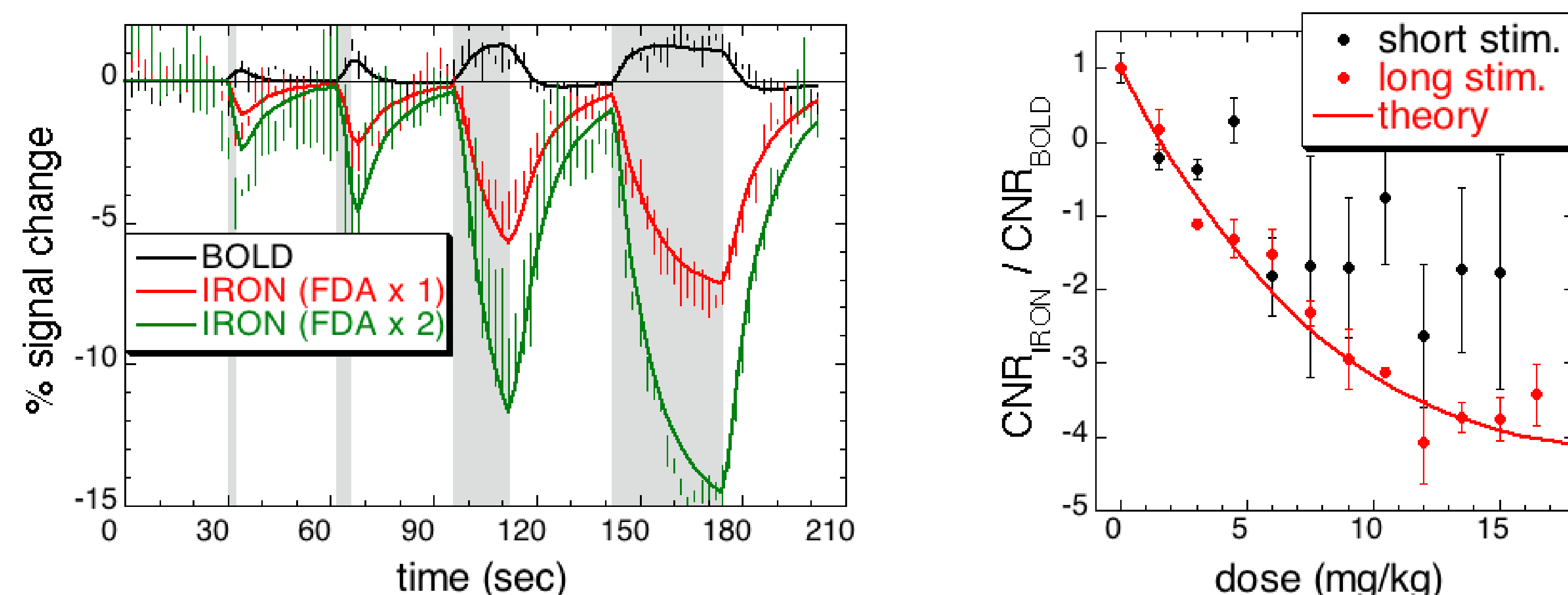


- The measured half life of the relaxation rate was significantly shorter (4.63 ± 0.04 hours) in the NHP than the blood half life reported in human subjects (15 hours). We are investigating reasons for this: 1) species difference, 2) modified NHP kinetics due to prior iron loading (previous experiments), 3) methodological differences between human and NHP measurements.

Contrast Agent

- Name: Feraheme
- Manufacturer: AMAG Pharmaceuticals, Inc. (Lexington, MA)
- Type: iron oxide, USPIO, coated with polyglucose sorbitol carboxymethylether
- Approval: June 30, 2009 by USA Food & Drug Administration
- Indications: Treatment of iron deficiency anemia in adult patients with chronic kidney disease
- Dose: 510 mg iron in 30 ml IV, followed by second injection 3 to 8 days later
- Adverse effects: 1.5% [7]
- blood half-life: 15 hours in humans
- cost: < 1\$/mg (USD)

Results: temporal response & CNR



The temporal response agrees with previous results in rats & monkeys. Shown are BOLD data (black) and the IRON responses using a dose of 7.5 mg/kg and 15 mg/kg. Solid lines are GLM regressors using parametric BOLD or IRON IRFs [5]

CNR versus dose for short (2 & 4 sec) and long (16 & 32 sec) stimuli, together with a theoretical calculation that doesn't account for different BOLD and IRON shapes (and so is appropriate for very long stimuli)

Methods: Acquisition

- Animal model: well-trained awake NHP (rhesus monkey) [4,5]
- Magnet: 3 Tesla Siemens Trio with AC88 gradient insert
- Iron doses: 12 mg/kg for half-life studies
0 to 16.5 mg/kg in steps of 1.5 mg/kg for CNR study
- Stimuli: Visual: letters & numbers embedded in noise pattern
- Durations: 2, 4, 16, and 32 seconds
- Averaging: 3 runs per dose

Methods: Analysis

- General linear model (GLM) using BOLD and IRON hemodynamic impulse response functions as previously described [5]
- To determine the **half life** of the relaxation rate, the signal average (DC term from GLM) was normalized by the pre-injection signal, and the agent-induced relaxation rate was plotted versus time
- For **CNR** measurements (T statistic), stimuli were divided into short (2 & 4 sec) and long (16 and 32 sec) using separate events in the GLM. Duration-dependent CNR was calculated due to the slow IRON response relative to the BOLD response.

Methods: Theory

- The relative CNR of BOLD and IRON methods was calculated following previous formulae [6].
- The largest theoretical uncertainty in the CNR ratio is the value of the basal BOLD-induced relaxation rate, which corresponds to "M" in the hypercapnia calibration literature [8]. We used a value of 4.1 sec^{-1} , consistent with previous reports [6] and well within the range of "M" values reported in human hypercapnia calibration measurements

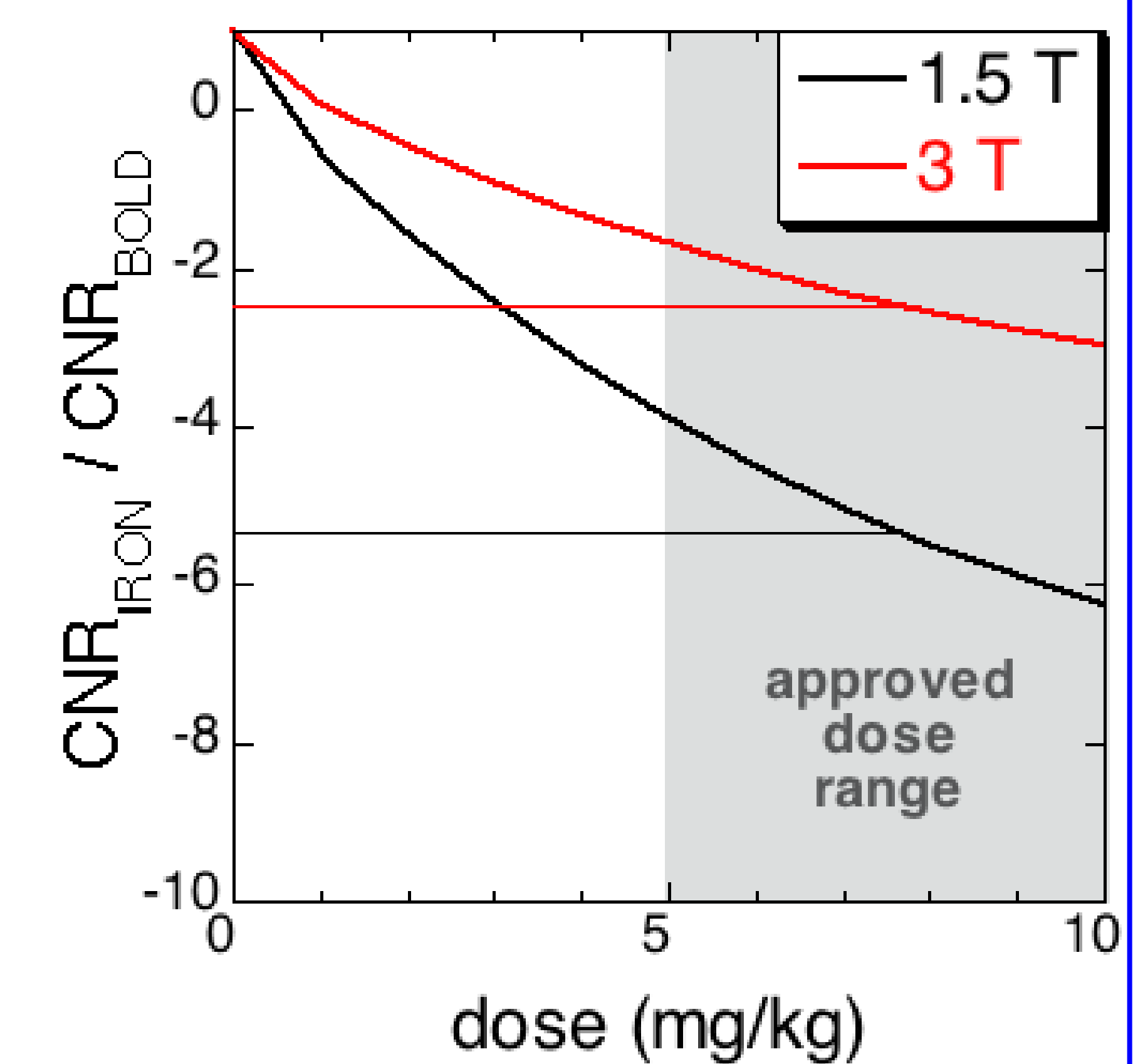
Prediction: human studies

Using experimentally validated calculations, we can predict the IRON to BOLD CNR ratio as a function of dose and magnetic field.

- The dose range assumes that the FDA-approved dose of 510 mg is injected into subjects within the weight range of 50-100 kg.

- The figure assumes an IRON echo time of 20 ms to reduce T2* artifacts and BOLD echo times that are matched to average T2* values at 1.5T (64 ms) and 3T (45 ms).

The FDA-approved dose of Feraheme should improve the CNR of fMRI by factors of about 5 at 1.5T and 2.5 at 3T.



Literature

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 - 3) Chen et al., JMRI 2001; 14(5):517
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Physiological basis for BOLD MR signal changes due to neuronal stimulation: separation of blood volume and magnetic susceptibility effects
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Repeated fMRI using iron oxide contrast agent in awake, behaving macaques at 3 Tesla
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