Probing the CBV-dominated impulse-response function to visual stimulation in humans in the presence of Ferumoxytol

Jacco A. de Zwart[1,*], Peter van Gelderen[1], Matthew Schindler[2], Pascal Sati[2], Jiaen Liu[1], Daniel S. Reich[2], Jeff H. Duyn[1]

[1]Advanced MRI section, LFMI, NINDS, and [2]Translational Neuroradiology section, NINDS, National Institutes of Health, Bethesda, MD, USA

[*]Jacco.deZwart@nih.gov

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Introduction

- Most functional MRI experiments exploit the blood oxygen-level dependent (BOLD) contrast mechanism
  - Increases in neuronal activation lead to local changes in:
    - Blood flow – CBF
    - Blood volume – CBV
    - Oxygen consumption – $CMRO_2$
  - The combined effect of these changes is a net decrease in the local concentration of deoxygenated hemoglobin, which is paramagnetic
    - Thus: activation → T_2^* ↑ → BOLD signal ↑
  - The domain in which CBF | CBV | $CMRO_2$ operate (arterial | capillary | venous), as well as the timing of these changes relative to stimulus onset, differs[1]
    - Understanding these differences is important for BOLD-fMRI interpretation

[1]Buxton, Neuroimage 2004:23, S220-S233

Introduction

- Ferumoxytol is a blood-pool-bound superparamagnetic iron-oxide particle
  - Approximately 17 – 31 μm in size
  - Half-life in blood exceeds 10 hours[1]
  - FDA-approved for treatment of iron deficiency anemia in chronic kidney disease

- Yields CBV-dominated contrast in humans[2]
  - In animals, its impulse-response function (IR) was shown to differ from BOLD IR[3]
  - Here, we measure CBV IR in human visual cortex and compare it to BOLD IR in the same volunteers
    - An efficient stimulus paradigm designed to measure IR while suppressing neuronal interactions was used

[1]Li, J Magn Reson Imaging 2005:21, 46-52
[2]Qiu, Neuroimage 2012:62, 1762-1731
[3]Silva, Magn Reson Med 2007:57, 1110-1118

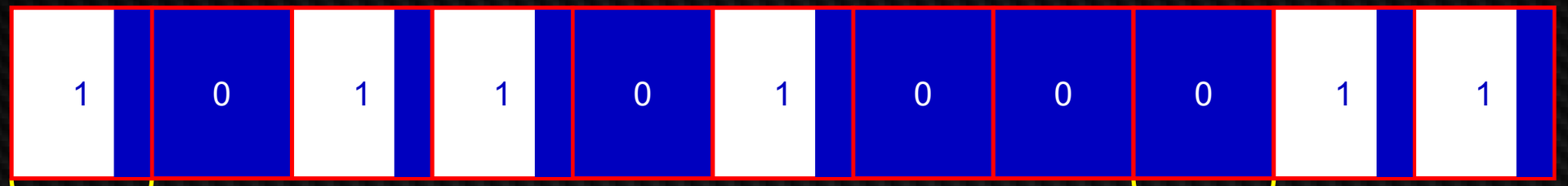
How was the impulse-response function measured?

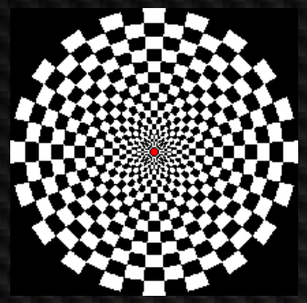
- We employed a binary m-sequence[1] for non-linear systems analysis
  - Pseudo-random sequence with a known, minimal auto-correlation behavior
    - Higher sensitivity than a random, e.g. Gaussian, paradigm
    - Allows studying interactions between individual events (stimuli) in the paradigm
- Kellman found that significant neuronal nonlinearities (interactions between subsequent stimuli events) exist in human visual experiments, but that they can be suppressed by using a brief inter-stimulus gap[2]

[1]Sutter, "A practical nonstochastic approach to nonlinear time-domain analysis", in: Advanced Methods of Physiological System Modeling (vol 1), Plenum, New York (1987) 303-315
[2]Kellman, Neuroimage 2003:19, 190-199

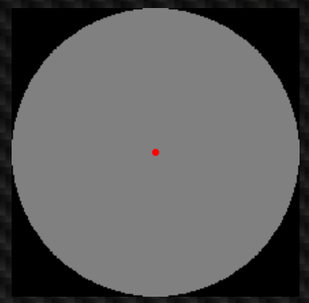
The binary m-sequence paradigm

- We used a 255-bin binary m-sequence
  - Each 'bin', or stimulus event, is 1-s duration, either '1' (stimulus) or '0' (rest)
    - Each stimulus-on bin ('1') ends with 200-ms rest to suppress interactions[1]
- Correlation-analysis yields the average impulse-response function as well as information about inter-stimulus interactions





'1' bin: 800-ms
7.5 Hz checkerboard
followed by 200-ms gap
(grey disk)

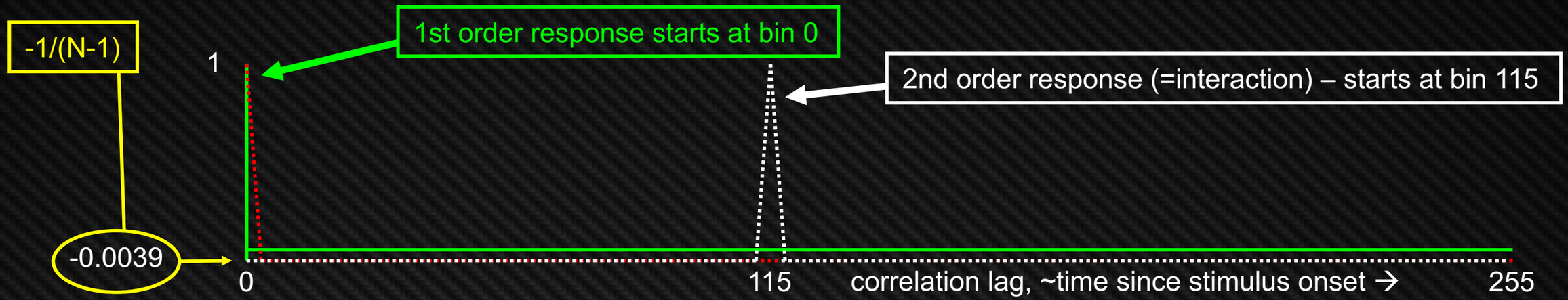


'0' bin:
grey disk throughout
(1000 ms)

[1]Kellman, Neuroimage 2003:19, 190-199

M-sequence: first and second order response

- Correlation analysis yields the average response to an 800-ms stimulus
  - Powerful additional feature: Multiplication of an m-sequence with a shifted version of itself yields another m-sequence with a different response offset (lag) in this correlation analysis
    - Interactions between stimuli, a.k.a. non-linear effects, are equivalent to such an m-sequence multiplication → interaction IRs are separated in analysis!
      - For the m-sequence used here: The 'IR' for the interaction between two consecutive events has an offset of 115 bins



USPIO fMRI response in rodents

- Work by Silva[1] in rats used a similar m-sequence design
  - Found CBV onset to precede BOLD
  - CBV IR narrower and faster than BOLD, but slow return to baseline
    - BOLD: 1.92 ± 0.22 s time to peak (TTP); 2.18 ± 0.14 s full width at half maximum (FWHM)
    - CBV: 1.65 ± 0.15 s TTP; 1.37 ± 0.11 s FWHM

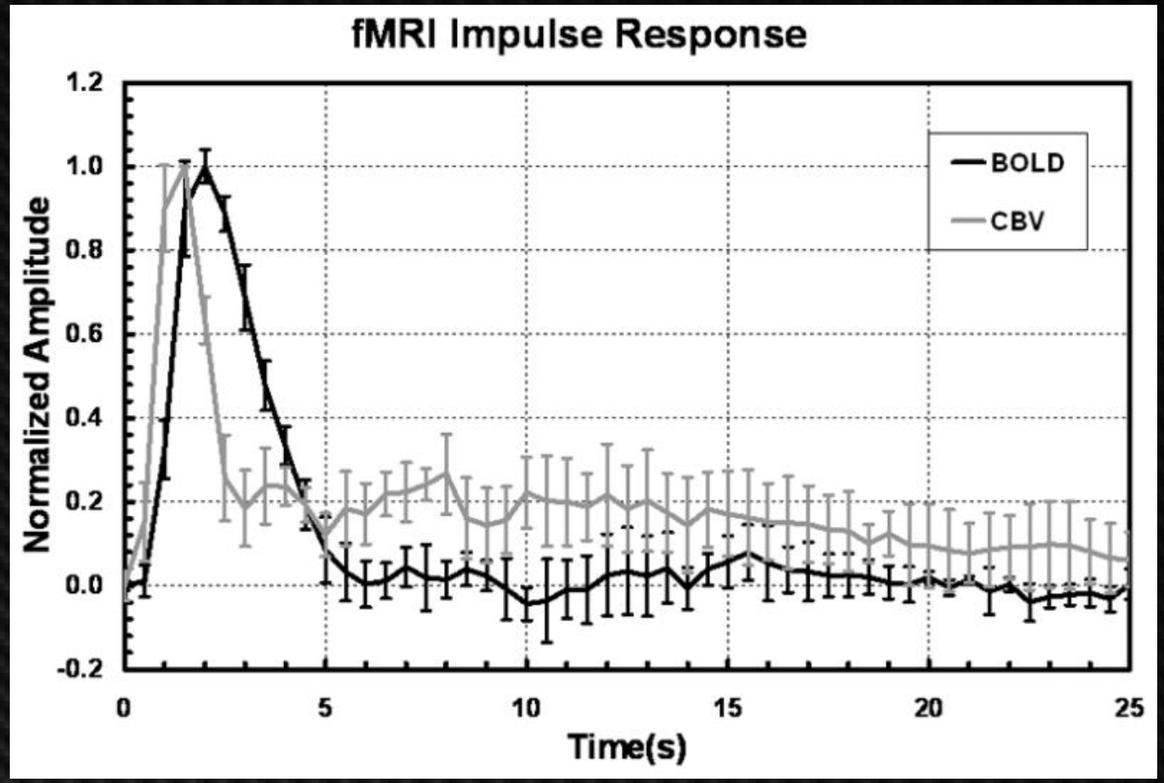
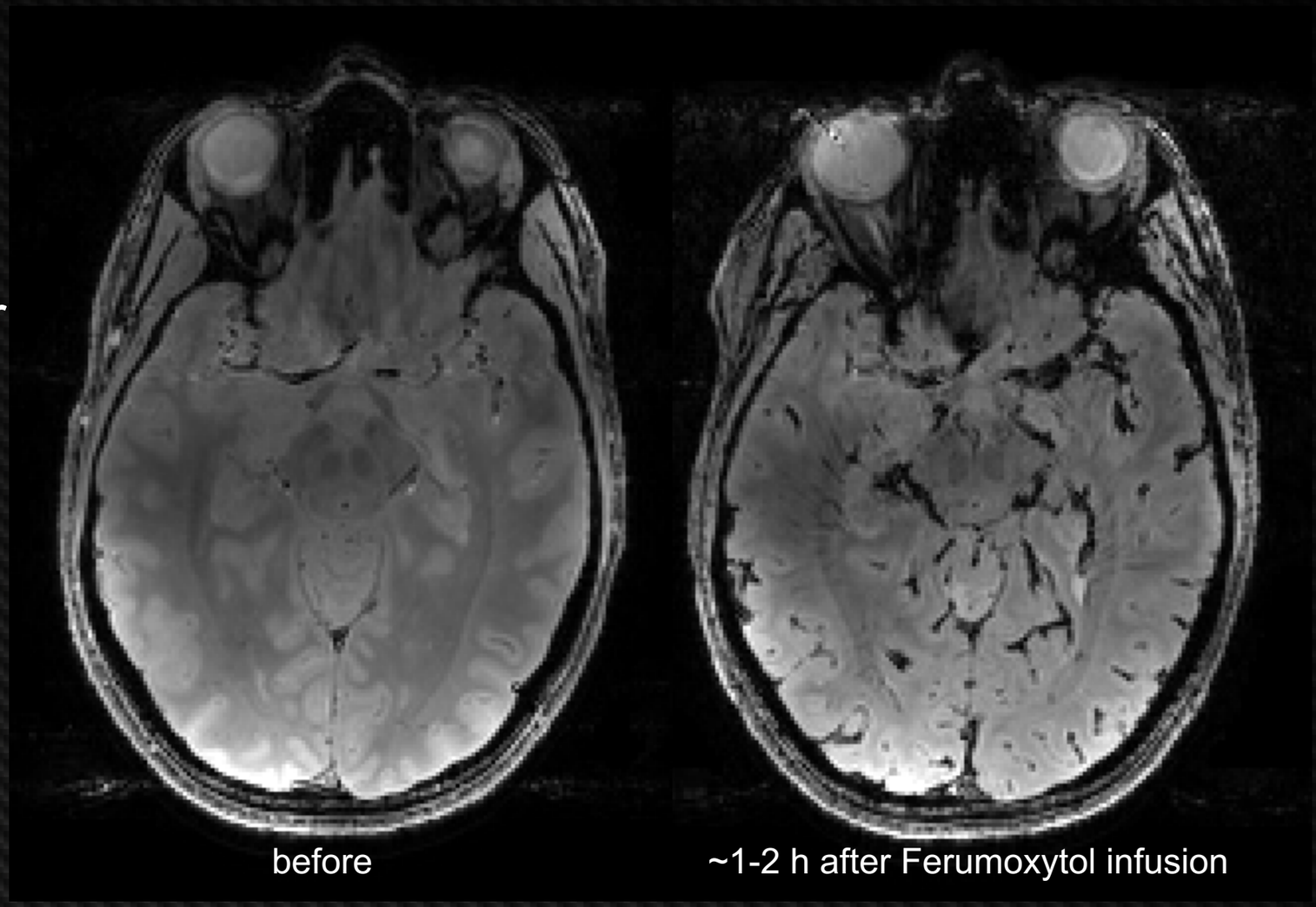


Figure 5 from Silva[1]: Average BOLD (black) and USPIO (grey) IR (n=5, rat)

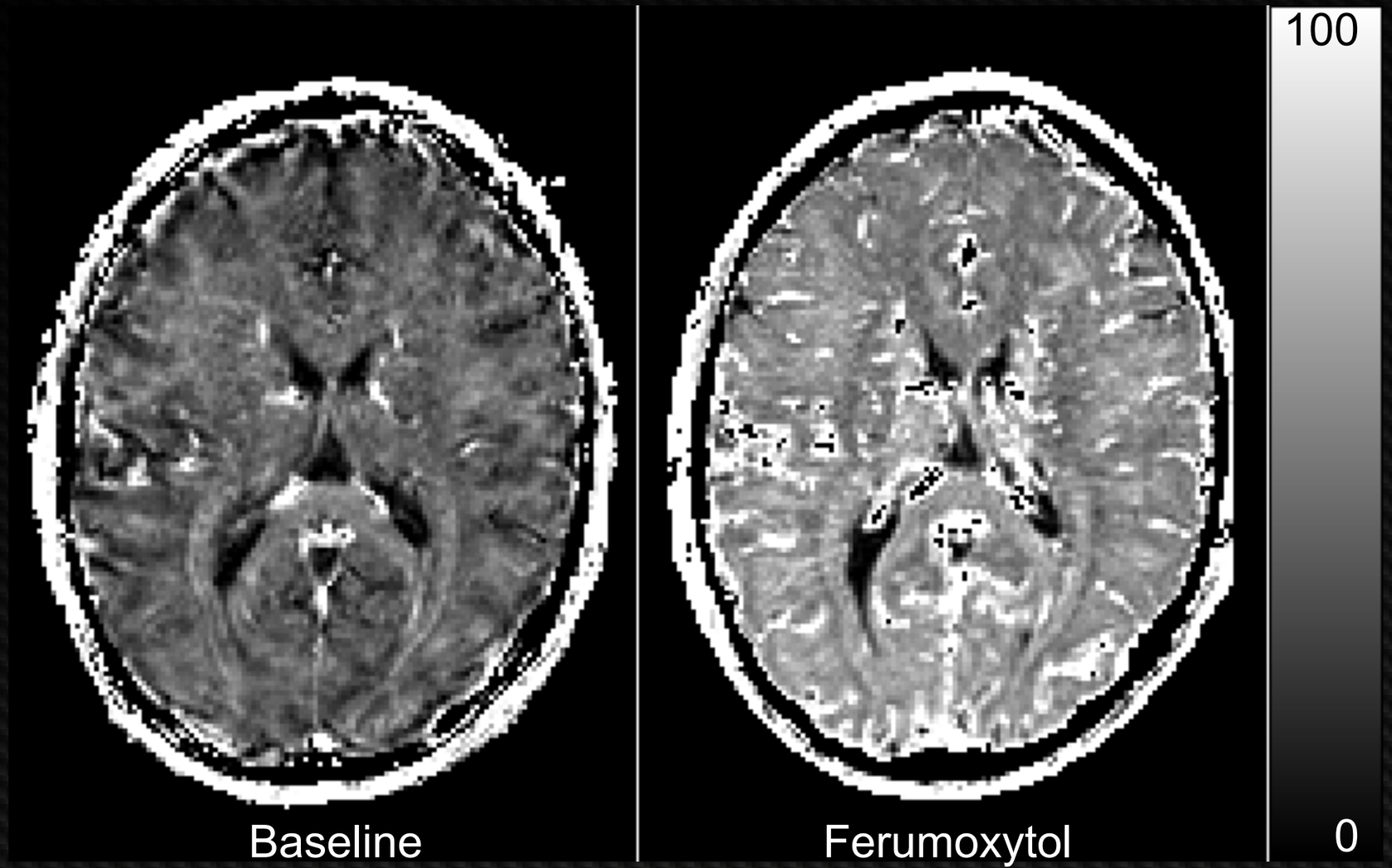
[1]Silva, Magn Reson Med 2007:57, 1110-1118

Ferumoxytol contrast in humans

- Ferumoxytol was infused in humans (n=5) as part of an unrelated study
  - Dose: 510 mg → 6.0 - 8.5 mg/kg
  - fMRI scans done 1 - 3 hours post-infusion
  - fMRI data from one volunteer discarded due to poor task performance (drowsiness) as indicated by response box data
    - Volunteers had to mark changes of the center dot color in stimulus images



Ferumoxytol contrast in humans – R_2*



Ferumoxytol leads to significant reduction of the T_2* relaxation time, especially in larger vessels

Example R_2* ($1/T_2$*) maps for one slice for the BOLD and Ferumoxytol experiment of one of the volunteers are shown here

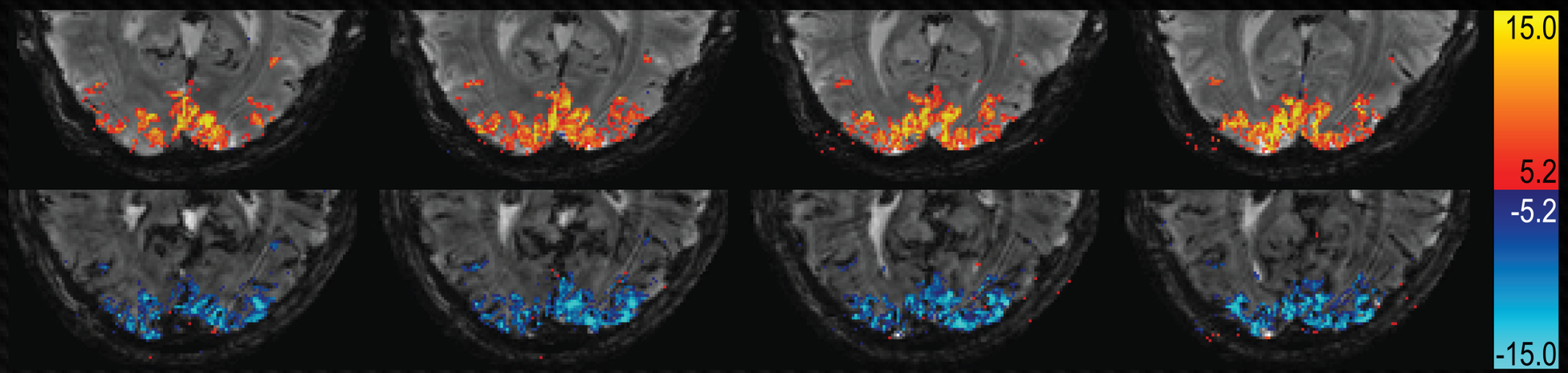
On average R_2* was 39.7 ± 24.6 s^{-1} for BOLD and 78.3 ± 47.7 s^{-1} for Ferumoxytol data in 8594 voxels from the functional ROI for 3 out of 4 volunteers
(A missing BOLD mGRE reference scan did not allow BOLD R_2* to be computed for the remaining volunteer)

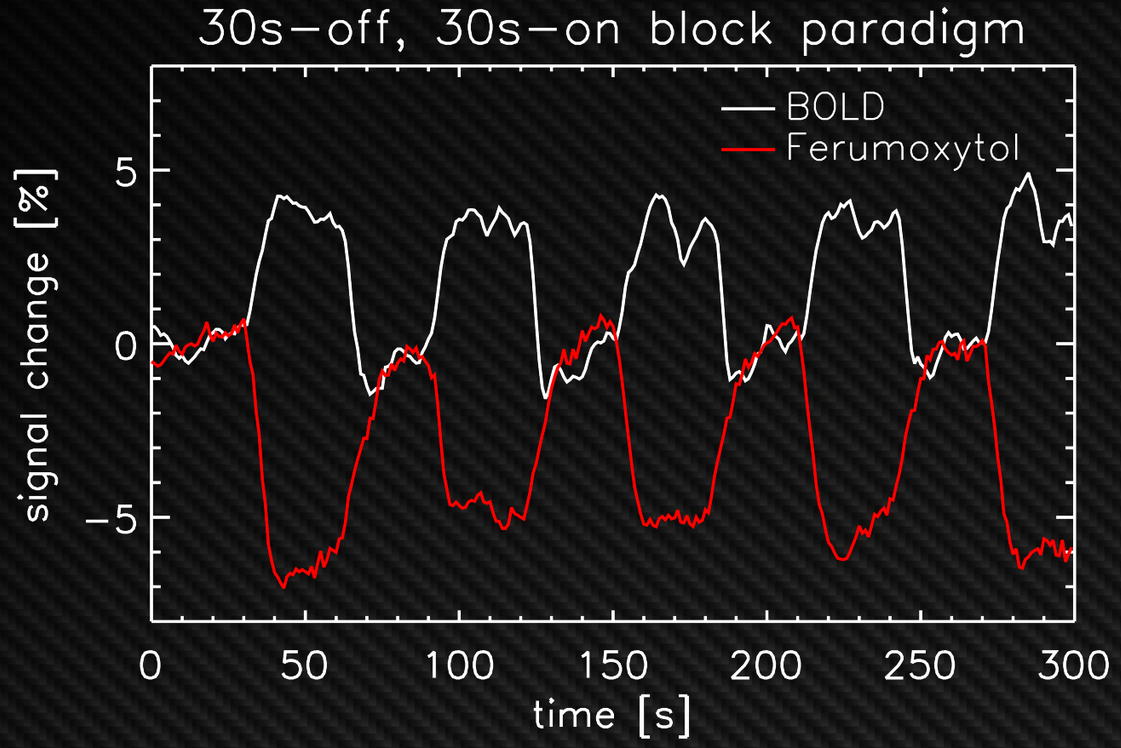
Experimental setup

- 7 Tesla MRI
- EPI with a relatively short echo-time was used – Ferumoxytol reduces T_2*
  - (1 volunteer): Rate-3 sense, 180 × 132, 18 slices, 24.5 ms TE, 1.2^3 mm^3
  - (3 volunteers): R-3 sense, 144 × 108, 28 slices, 16.2 ms TE, 1.5 × 1.5 × 1.2 mm^3
- 5-min "30 s off / 30 s on" block paradigm as a localizer, 1-s TR
- 10-min m-sequence runs, 600 repetitions @ 1-s TR
  - 255-bin m-sequence preceded by 45 extra volumes for steady state
    - The last 45 events of the same m-sequence were used for this
  - Inverse repeat: This 300-event paradigm is repeated with 'on' and 'off' bins swapped to further help identify inter-stimulus interactions[1]

[1]Kellman, Neuroimage 2003:19, 190-199

Block paradigm results

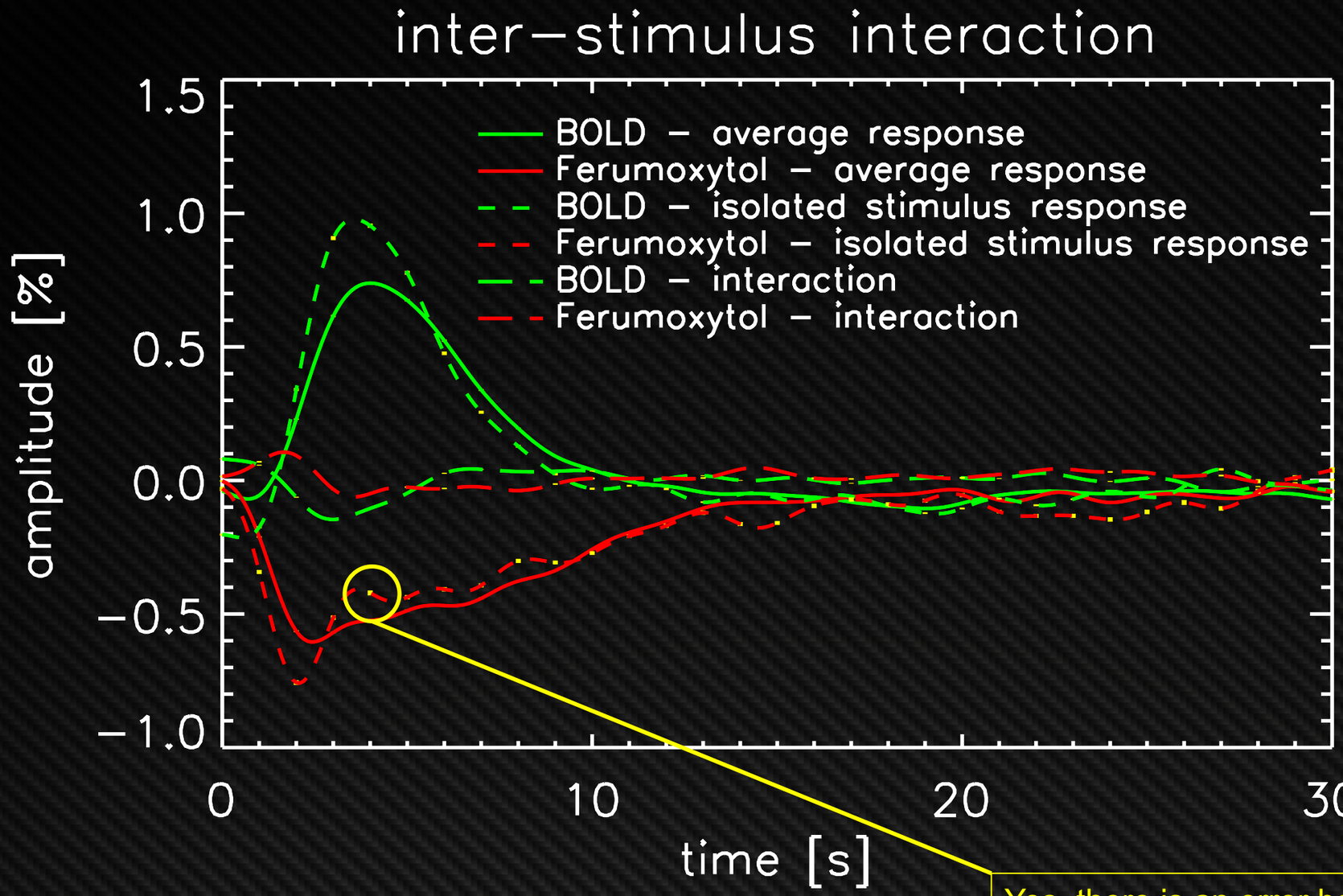




Data from all block- and m-sequence scans were registered to the 10th volume in the BOLD block paradigm scan

Mean response in the 11715 voxels (2929 ± 730) that were significantly activated in both the BOLD and Ferumoxytol block paradigm experiments in the 4 volunteers (=functional ROI) – Note that Ferumoxytol yields a signal-decrease on activation (activation → CBV ↑ → signal ↓)

Observed responses – correcting for interactions



- The direct result of the correlation analysis is the mean response to all events in the experiment ('average response')
  - Some events have a stimulus directly before it (two consecutive m-sequence '1' bins), others do not ('0' followed by '1' bin)
- The interaction term (@lag 115 in correlation result) can be used to correct the average response to obtain an isolated stimulus response (no stimulus in the bin before it)
  - Interaction terms are small for both BOLD and Ferumoxytol, ~15% of the 'average' response

Yes, there is an error bar here! (SE over 11715 voxels)

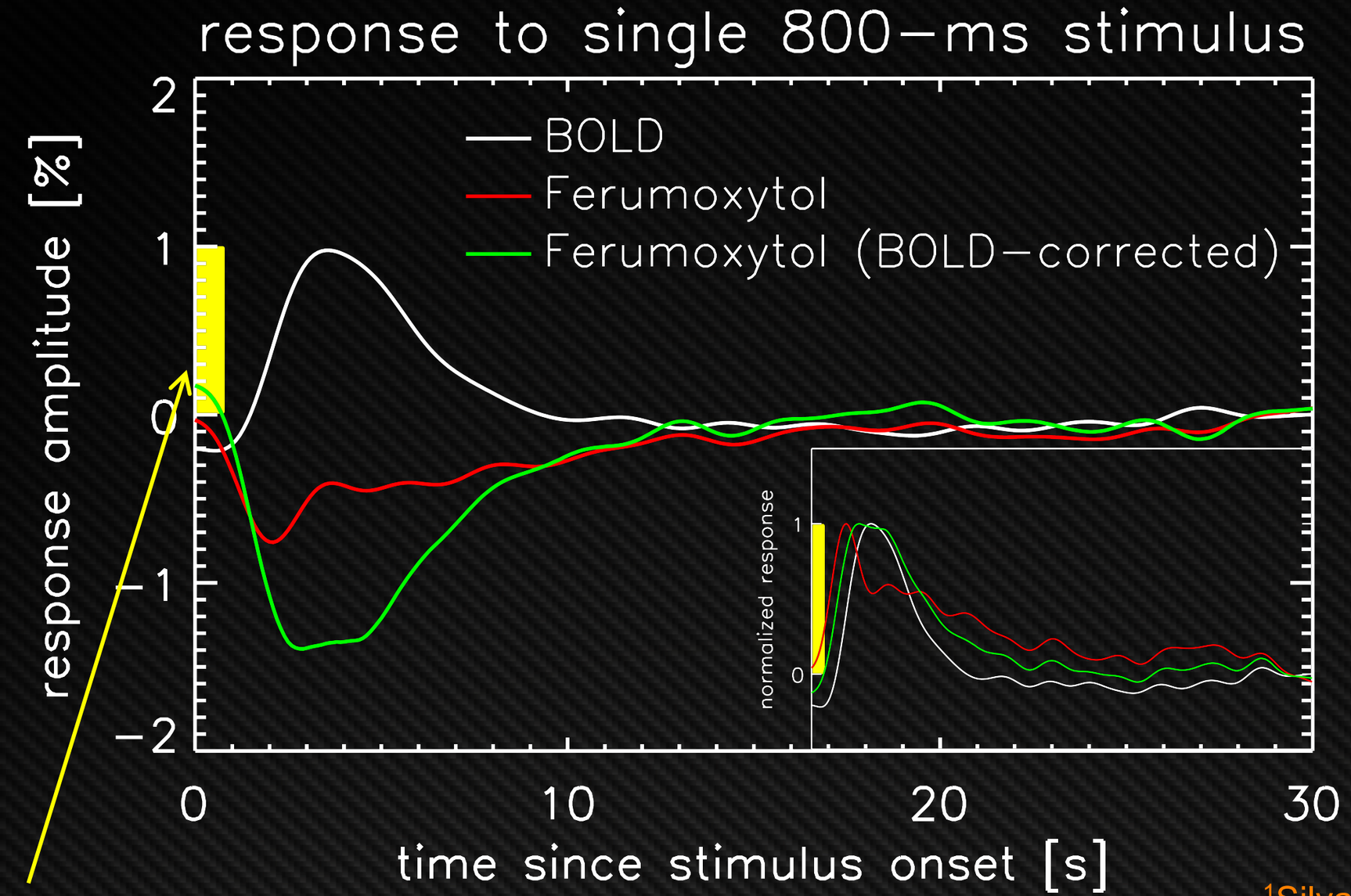
Correcting for BOLD contribution to Ferumoxytol data

- The BOLD effect still contributes to the Ferumoxytol data
  - Effect size varies from voxel-to-voxel, depending on the local R_2*
    - The BOLD data for the same volunteer can be used to compute task-induced ΔR_2* for each voxel
    - Assuming identical task performance in BOLD and Ferumoxytol experiments, task-induced BOLD ΔR_2* should be identical in the Ferumoxytol data
    - The corresponding signal change can then be computed
      - Here, TE was identical in BOLD and Ferumoxytol experiments, so the correction simplifies to:

$$IR_{Feru,\,corrected} = IR_{Feru} - \frac{A_{BOLD}}{A_{Feru}} \cdot IR_{BOLD}$$

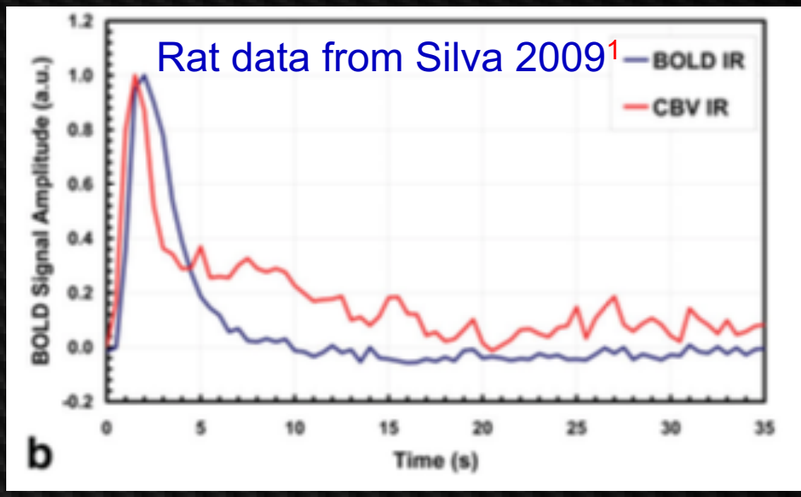
where A_{BOLD} and A_{Feru} are the mean signal level in the respective voxel time courses

BOLD versus Ferumoxytol impulse-response



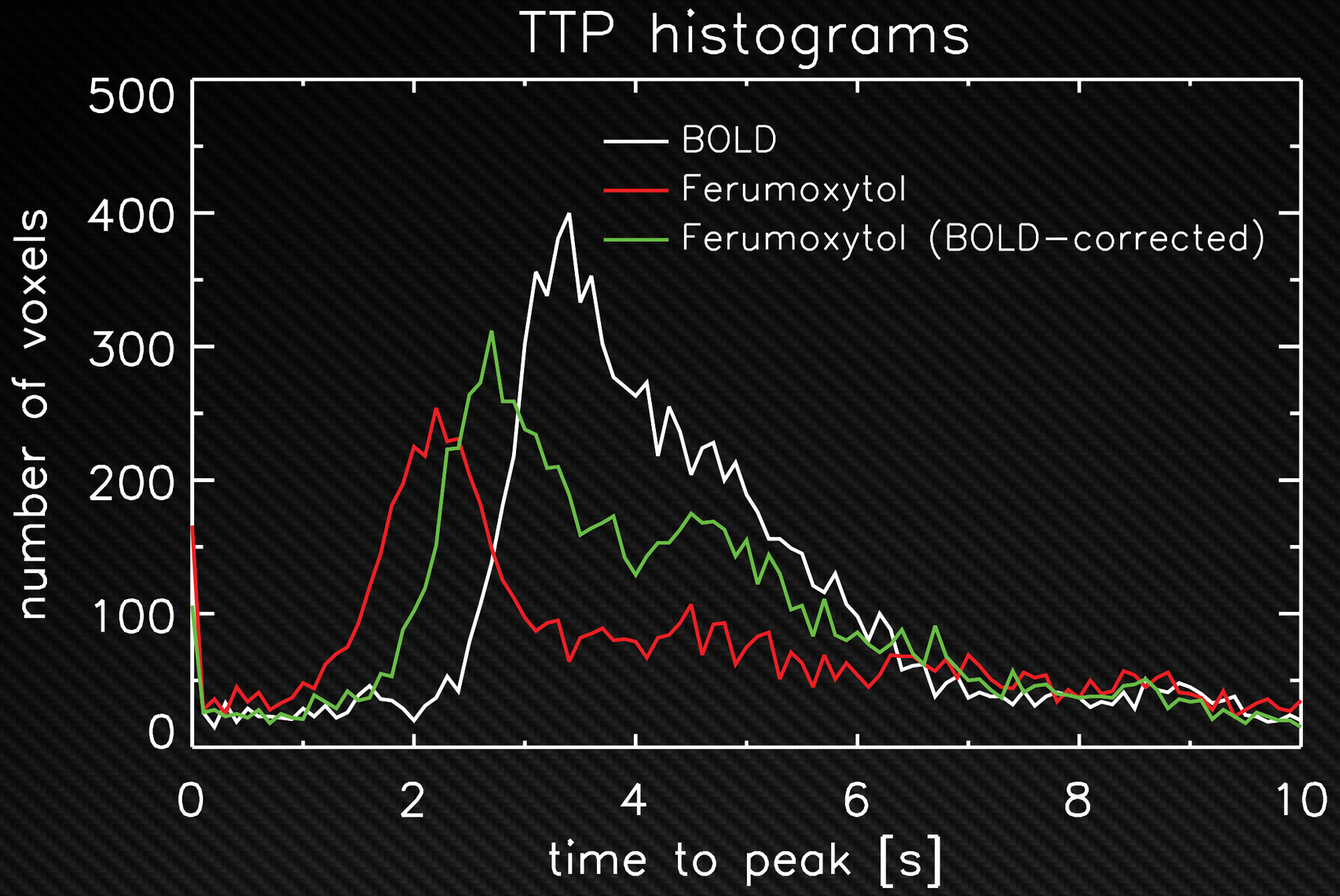
Measured impulse-response functions to an isolated stimulus, showing BOLD increase (white) and Ferumoxytol decrease (red)

BOLD is still present in Ferumoxytol data, this opposing contrast can be corrected for (green) on a voxel-by-voxel basis since we also have BOLD-only data



[1]Silva, Magn Reson Med 2007:57, 1110-1118

Time to peak histograms



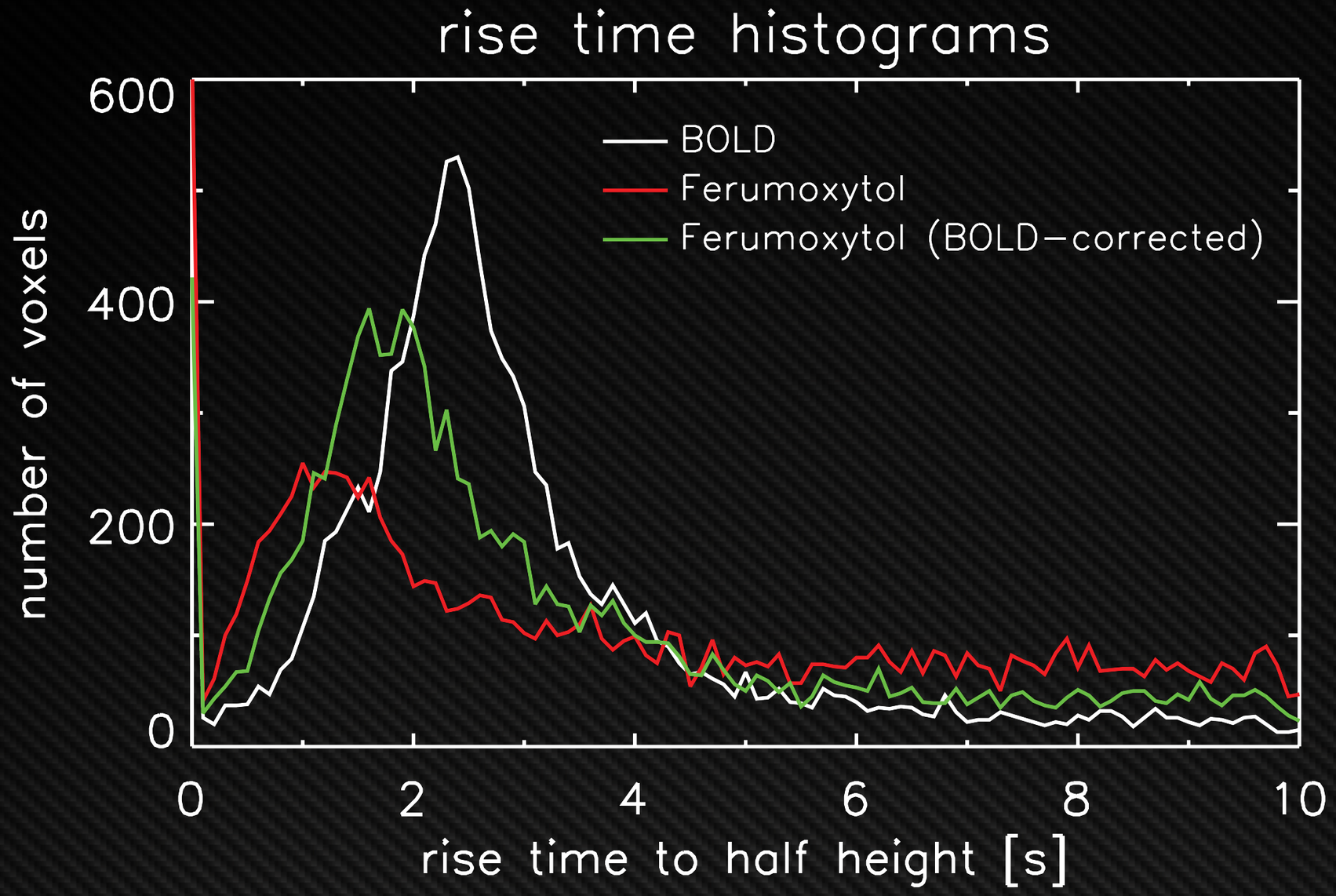
This plot shows histograms for the time to peak (time from stimulus onset to IR maximum) for the 11715 voxels from 4 volunteers for BOLD and (corrected) Ferumoxytol

A large pool of Ferumoxytol voxels shows notably shorter TTP than BOLD, however wider spread of TTP is found than for BOLD

Possible causes:

- Sub-optimal correction for BOLD, in combination with a relative BOLD contribution that varies on a voxel-by-voxel basis (depending on local vasculature)
- Different TTP pools for Ferumoxytol in the arterial and venous domain?

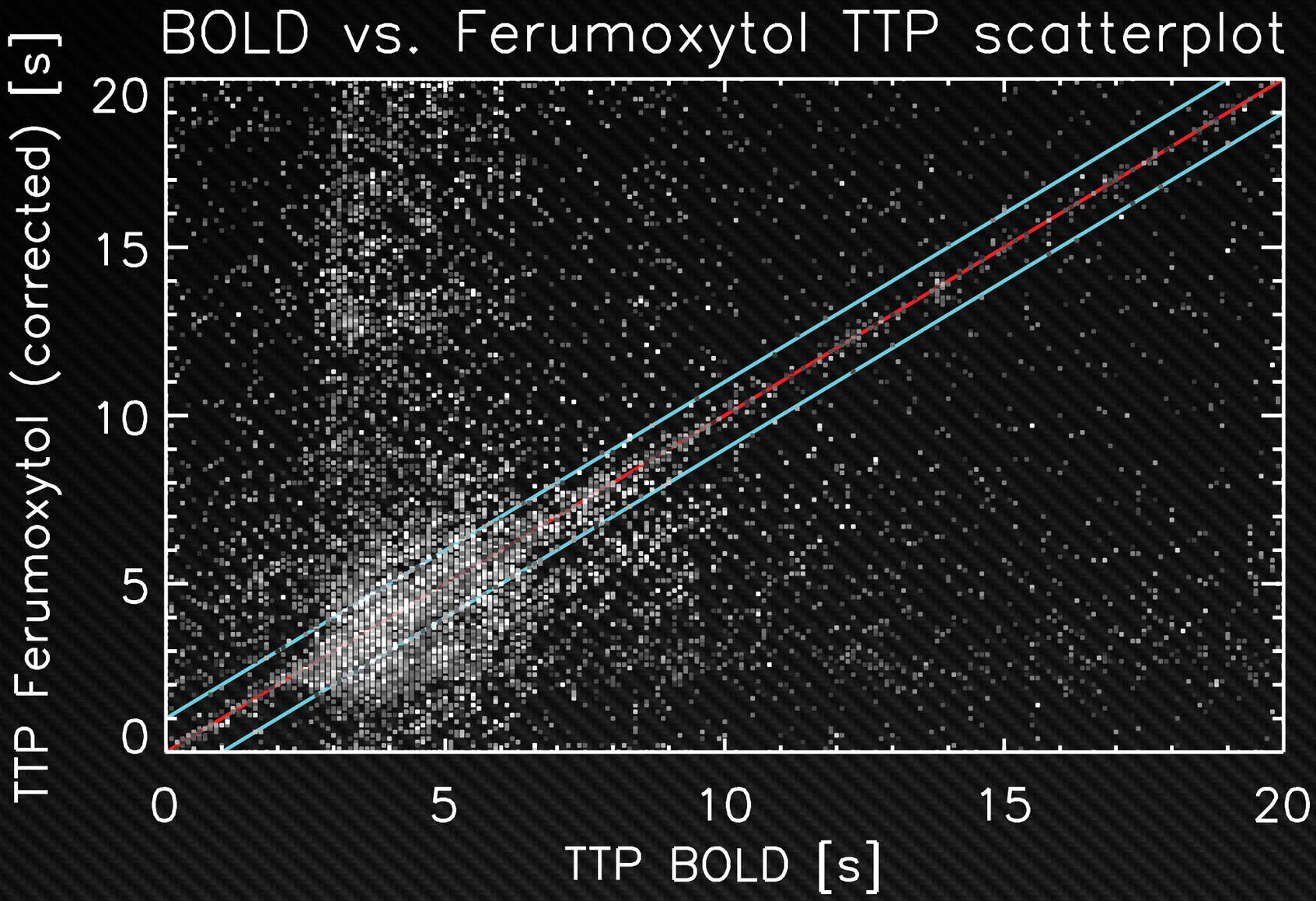
Rise time histograms



This plot shows histograms of the rise-time for the 11715 voxels from 4 volunteers for BOLD and (corrected) Ferumoxytol

Rise time, defined as the time from stimulus onset to the time IR crosses half of peak height, shows similar behavior as TTP

Time to peak – BOLD versus Ferumoxytol



Scatter plot of BOLD versus Ferumoxytol TTP for all 11715 voxels from 4 volunteers

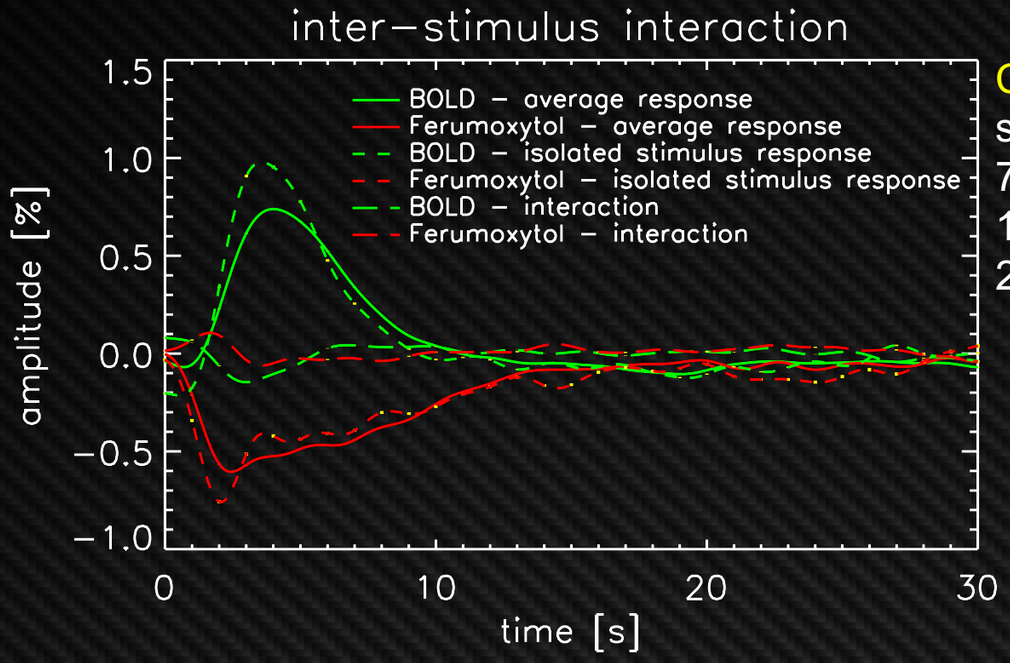
Grey level indicates significance of the response in that voxel (whiter = more significant); The red line shows identity, light blue lines a 1 second in- and decrease in TTP, respectively

This further illustrates that Ferumoxytol TTP is on average faster than BOLD TTP; no clear separation of different 'pools' is evident

Possible errors in image registration, as well as in the BOLD correction of Ferumoxytol data, could contribute to the noise (and lack of distinct features?)

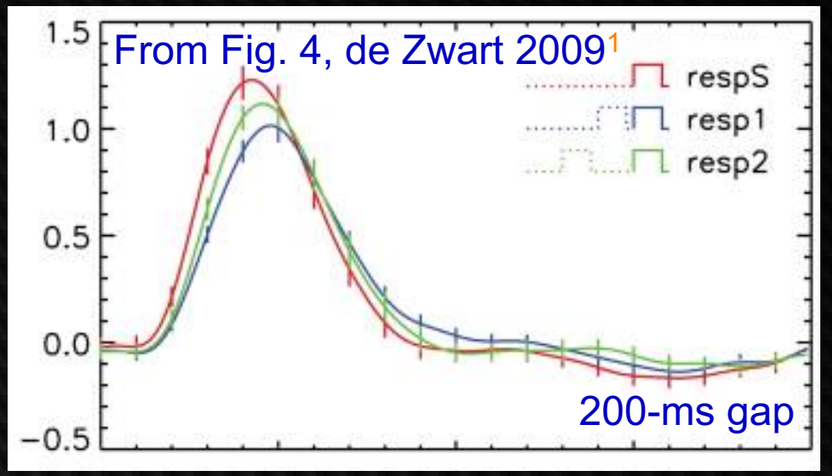
Comparison with de Zwart et al., 2009[1]

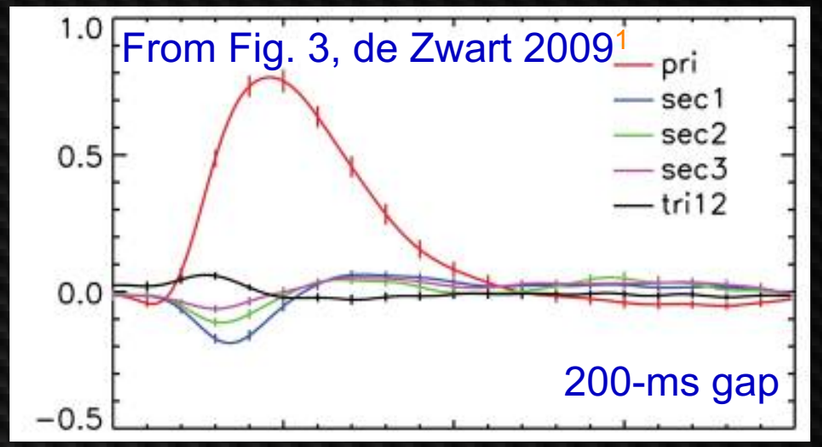
The relative size of the interaction term for BOLD data found in these 7 T experiments is similar to our earlier 3 T BOLD-only data[1], as is their effect on IR shape and timing: A preceding stimulus causes delay and widening of BOLD IR, presumably a vascular effect.



Current study: Human visual stimulus; BOLD and USPIO; 7 Tesla; 1.5 × 1.5 × 1.2 mm^3; 16 ms TE; m-sequence with 200-ms gap

2009 study: Human visual stimulus; BOLD only; 3 Tesla data; 1.6 × 1.6 × 2.0 mm^3; 44 ms TE; m-sequence with 200-ms gap





[1]de Zwart, Neuroimage 2009:47, 667-677

Discussion

- Ferumoxytol fMRI in humans confirms findings from rat somatosensory data
  - CBV-dominated fMRI impulse response TTP is faster than BOLD
  - CBV response appears bi-phasic, a fast peak followed by a long tail (slow return to baseline)
  - This bi-phasic response could not be readily attributed to two distinct pools (e.g. arterioles and venules)

Discussion

- Nonlinearities in SPIO fMRI are on the same scale as for BOLD
  - ~15% of main response amplitude
  - Presence of a preceding stimulus increases response latency and reduces response amplitude for both BOLD and Ferumoxytol
    - Consistent with a vascular origin of these residual interaction effects[1]

[1]de Zwart, Neuroimage 2009:47, 667-677