Comparison of BOLD and CBV impulse-response in the human visual system in the presence of Ferumoxytol

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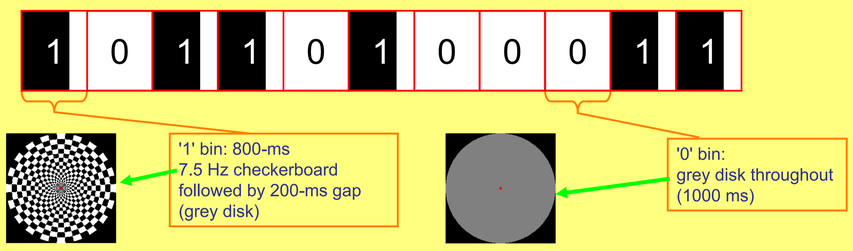
Advanced MRI

Introduction

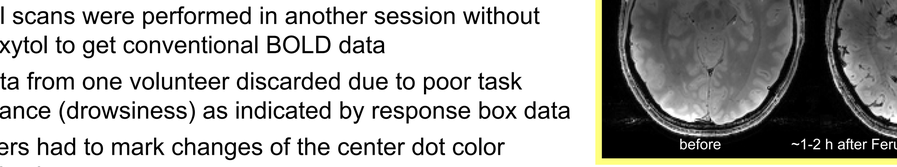
- Most functional MRI experiments exploit the blood oxygen-level dependent (BOLD) contrast mechanism
  - Increases in neuronal activation lead to local changes in:
    - Blood flow – CBF
    - Blood volume – CBV
    - Oxygen consumption – $CMRO_2$
  - The combined effect of these changes is generally a net decrease in the local concentration of deoxygenated hemoglobin, which is paramagnetic, thus creating a positive BOLD signal change
    - 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
- Ferumoxytol is a blood-pool-bound superparamagnetic iron-oxide particle
  - Approximately 17 – 31 µm in size
  - Half-life in blood in humans exceeds 10 hours[2]
  - It is FDA-approved for treatment of iron deficiency anemia in chronic kidney disease
- Intravenous Ferumoxytol yields CBV-dominated contrast in humans[3]
  - In animals, impulse-response function (IR) with iron oxide present was shown to differ from BOLD IR[4]
  - We measured Ferumoxytol IR in human visual cortex and compare it to BOLD in the same volunteers
  - A stimulus paradigm designed to measure IR while suppressing neuronal interactions was used

How was the impulse-response function measured?

- We employed a binary m-sequence[5] for non-linear systems analysis
  - This is a pseudo-random sequence with a known, minimal auto-correlation behavior
  - An m-sequence based paradigm has a higher sensitivity than a random, e.g. Gaussian, paradigm
  - It 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[6]
- 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 stimulus to suppress interactions[1] (the 'gap')



- 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[4] in rats used a similar m-sequence design
  - They found CBV onset to precede BOLD
  - CBV IR was narrower and faster than BOLD, but showed a 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

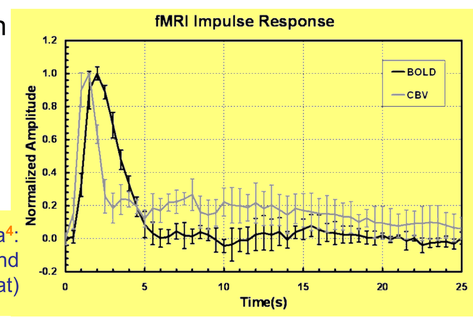
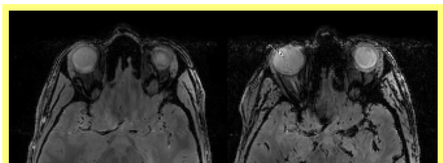


Figure 5 from Silva[4]: Average BOLD (black) and USPIO (grey) IR (n=5, rat)

Ferumoxytol contrast in humans

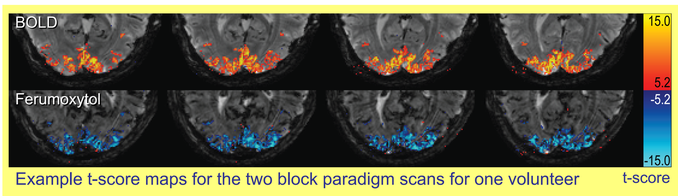
- Ferumoxytol was infused in humans (n=5) as part of an unrelated, IRB-approved study
  - Dose: 510 mg → 6.0 - 8.5 mg/kg
  - fMRI scans were done 1 — 3 hours post-infusion
  - Identical scans were performed in another session without Ferumoxytol to get conventional BOLD data
  - fMRI data from one volunteer 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



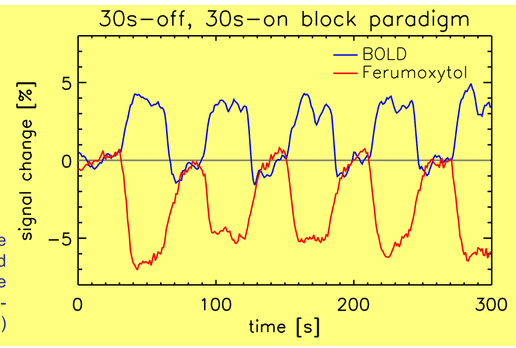
Experimental setup

- 7 Tesla MRI – EPI with a relatively short echo-time was used since Ferumoxytol reduces T_2*
  - (1 volunteer): Rate-3 SENSE, 180 × 132 matrix size, 18 slices, 24.5 ms TE, 1.2^3 mm^3 voxels
  - (3 volunteers): Rate-3 SENSE, 144 × 108 matrix size, 28 slices, 16.2 ms TE, 1.5 × 1.5 × 1.2 mm^3
- We acquired a 5 min "30 s off / 30 s on" block paradigm, 1 s TR, to determine functional ROI
- We acquired a 10 min m-sequence run, 600 repetitions @ 1 s TR
  - This consisted of a 255-bin m-sequence preceded by 45 extra volumes for steady state
    - The last 45 events of the same m-sequence were used for those preceding events
  - Inverse repeat: This 300-event paradigm is repeated with 'on' and 'off' bins swapped to further help identify inter-stimulus interactions[6]
  - All block- and m-sequence scans were registered to the 10th volume in the BOLD block paradigm scan
  - Results are averaged over functional ROI voxels

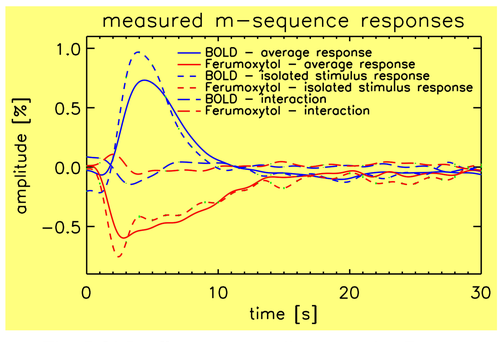
Results



Example t-score maps for the two block paradigm scans for one volunteer



Mean response in the 11715 voxels (2929 ± 730 per subject) 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 ↓)

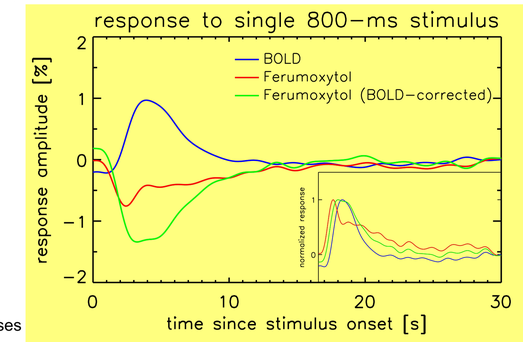


- The direct result of the correlation analysis is the mean response to all events in the experiment ('average response')
- Some events have a stimulus directly before it (two consecutive m-sequence '1' bins), others do not ('0' followed by '1' bin)
- The interaction term (@lag 115 in correlation result) 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

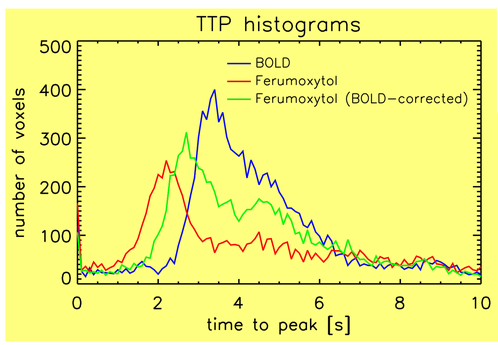
- The BOLD effect still contributes to the Ferumoxytol data
  - Effect size varies from voxel-to-voxel, depending on the local R_2*
  - The BOLD data for the same volunteer can be used to compute task-induced ΔR_2* for each voxel
  - Assuming identical task performance in BOLD and Ferumoxytol experiments, 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



Measured impulse-response functions to an isolated stimulus, showing BOLD increase (blue), Ferumoxytol decrease (red) and BOLD-corrected Ferumoxytol response (green). The insert shows normalized versions of these responses to illustrate their relative timing.



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

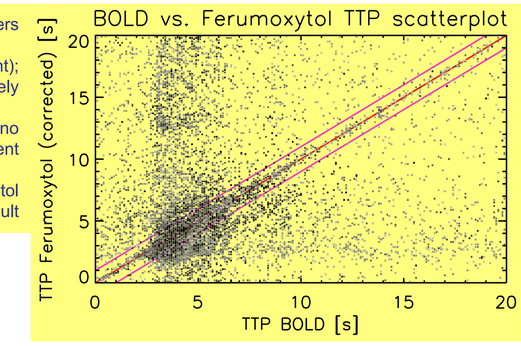
Possible causes:
- Sub-optimal correction for BOLD, in combination with a relative BOLD contribution that varies on a voxel-by-voxel basis (depending on local vasculature)
- Different TTP pools for Ferumoxytol in the arterial and venous domain?

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

Grey level indicates significance of the response in that voxel (darker is more significant); The red line shows identity, pink 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 have significantly affected this result



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)
- 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[7]

References

[1]Buxton, Neuroimage 2004:23, S220-S233
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[5]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
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