Evidence of the BOLD Post-Undershoot Rebound

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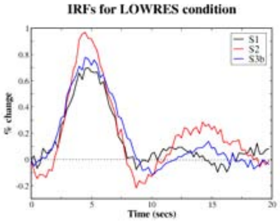
Introduction: Neural activity causes changes in blood oxygenation and cerebral blood flow that are detectable with MRI. Accurate characterization of the BOLD hemodynamic response function (HRF) is important to understand neuro-vascular coupling. Aside from the well-characterized positive response to event-related stimuli, the HRF robustly displays a post-stimulus undershoot and to a lesser degree an initial dip. It is assumed that the HRF returns to baseline values after the post-stimulus undershoot and thus is normally modeled using the difference of two Gamma-Variate functions. We have consistently observed a post undershoot "rebound" effect associated with a very brief stimulus. In this abstract, we empirically characterize this additional dynamic attribute of the HRF and propose models that might explain it.

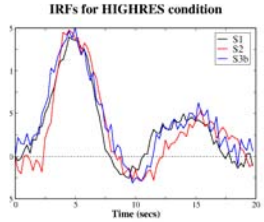
Methods: Imaging Hardware: 3T General Electric VH/3 whole body MRI scanner equipped with 16 channel digital receivers and a 16-element receive-only brain surface-coil array. Single shot, full k-space gradient recalled EPI was used for all functional scans. Brief visual stimuli evoked BOLD responses in 4 subjects: S1, S2, S3 and S4. Subjects S1, S2 and S3a underwent scanning for four conditions: LOWRES, HIGHRES, DECON and BLOCK. Subjects S3b and S4 experienced four different conditions (different day for S3b): ISI60, P16.8, P40 and P60. Localization of the visual cortex was performed prior to main experiment using an 8Hz flashing checkerboard presented in a block design (30s OFF/30s ON, TR=1s, TE=27ms, matrix=64x64, FOV/slice = 24cm/4mm, 8 axial slices, flip angle=70°, 180 volumes). The subjects wore LCD goggles that remained closed for the majority of the experiment. Visual stimuli were presented by opening the goggles with a current pulse to reveal a static checkerboard.

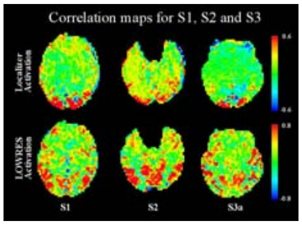
For S1, S2 and S3a, identical scanning parameters were used for all conditions - TR=250ms, TE=27ms, matrix=64x64, FOV/slice = 24cm/4mm, 4 slices, flip angle=40°. LOWRES: visual stimuli lasted 23ms and were presented with an ISI=20s. Three runs lasting 310s each were acquired. HIGHRES: slice thickness changed to 2mm for this condition alone. Identical visual stimuli to the LOWRES condition. DECON: jittered visual stimuli lasting 23ms were presented during one run lasting 310s yielding 60 events – average ISI=5s, range=2s-8s. BLOCK condition: visual stimuli lasting 23ms were presented in one run lasting 310s with an ISI=250ms in a block design fashion (30s ON/30s OFF).

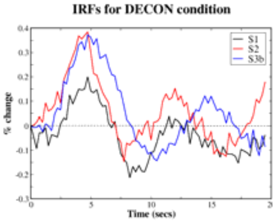
For S3b and S4, identical scanning parameters were used for all conditions - TR=250ms, TE=30ms, matrix size=64x64, FOV/slice = 24cm/4mm, 4 slices, flip angle=30°. ISI60: visual stimuli lasting 16.8ms with an ISI=60s were presented over 4 runs, each lasting 10mins. P16.8, P40 and P59: visual stimuli lasting 16.8ms, 40ms and 59ms, respectively, were presented with an ISI=20s for 10mins.

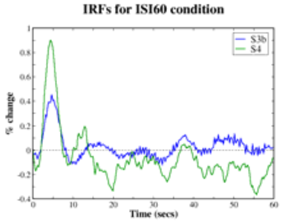
The fMRI data for each condition were converted into percentage change and quadratically detrended. Impulse response functions (IRFs) were obtained for each condition by simply averaging the data between one event to the next. Activation maps for each condition were calculated by selecting voxels whose first 8 seconds of IRF had a correlation value of greater than 0.8 with a standard gamma-variate canonical HRF. The IRFs were rescaled to make their first timepoint zero (with the exception of the ISI60 condition: to reduce noise the mean of the 5 seconds preceding the scan was scaled to zero). Average IRFs were determined for each condition by calculating the mean response across the appropriate activation map.


IRFs for LOWRES condition


IRFs for HIGHRES condition


Correlation maps for S1, S2 and S3


IRFs for DECON condition


IRFs for ISI60 condition

Results and Discussion: A post-undershoot rebound response was visible in all subjects peaking between 12.1 and 14.5 seconds after stimulus onset (in the LOWRES condition) before returning towards baseline. An increase in resolution reduces partial volume effects and amplified both the first overshoot and the rebound response. Also, the ratio of main response height to rebound height (using the undershoot depth as a baseline) increased significantly from an average of 0.32, 0.38 and 0.34 to 0.49, 0.48 and 0.50 for S1, S2 and S3a respectively. The IRFs for each subject were rendered almost identical in all timings and response heights by this increase in resolution. The activation maps determined from these conditions bear little resemblance to those determined by the functional localizer with minimal overlap between the two. This suggests that the largest response to the brief visual stimuli is not found in the capillaries of the visual cortex but in larger vessels further upstream.

The rebound response is still visible after deconvolution of a jittered event-related design. However, convolving a smoothed version of the LOWRES IRF with a block design to make a regressor leads to higher correlation values in the BLOCK condition in only one subject, S3a, compared with regressors derived from a Gamma-Variate and the difference of two Gamma-Variates. This is unsurprising since the most significant responses to the block stimulation are found mainly in the localizer areas, which differ significantly from the LOWRES activation maps. Evidence of the rebound response in the LOWRES condition is poor in voxels deemed active by the BLOCK condition.

Whether the post-undershoot rebound depends on stimulus length is inconclusive. No consistent pattern of significant differences was found across the two subjects. It is probable that the post-undershoot rebound is not affected by stimulus duration (for stimulus <60ms long).

The ISI60 condition demonstrates that the response to brief stimuli lasts longer than previously anticipated. After the post-undershoot rebound the signal does not immediately return to baseline. Between 20 and 60 seconds after the event, fluctuations of ~0.08Hz are visible with definite positive lobes observable at approximately 26 and 38 seconds. Two possible explanations considered here are: 1) a brief stimulus produces a vascular response with a feedback mechanism that attempts to damp the signal; 2) the phases of known low-frequency resting state fluctuations are reset by the event to coincide with each other and thus these low-frequencies are visible after averaging. Adding a feedback term to the balloon model may help investigate if the first idea is feasible. More evidence exists for the second explanation in this data: the fluctuations observed after the post-undershoot are in the correct frequency range ~0.1Hz and there are similarities between the LOWRES and resting-state network activation maps.

Conclusions: Using a high SNR setup and very brief visual stimuli, a post-undershoot rebound is visible in all subjects and it's effects are seen well beyond 20 seconds. This response is not evident in the visual cortex (defined in the standard way by using a block design) suggesting that a different vascular mechanism is at work, possibly linked to resting state low-frequency fluctuations.