Difference in temporal dynamics of positive and negative BOLD responses

J. L. Gardner[1,2], P. Sun[2,3], R. A. Waggoner[3], K. Ueno[3], K. Tanaka[3], K. Cheng[3]

[1]Center for Neural Science and Department of Psychology, New York University, New York, NY, United States, [2]Japan Society for the Promotion of Science, Postdoctoral, Fellow, Japan, [3]RIKEN Brain Science Institute, Wakoshi, Saitama, Japan

ABSTRACT: We have studied the dynamics of positive and negative transient BOLD responses in the same voxels and found that they have consistently different dynamics. We evoked positive and negative responses in retinotopically defined V1 by either incrementing or decrementing the contrast of a visual stimulus from a baseline contrast. While the negative BOLD responses were lagged in comparison to the positive responses, they had quicker dynamics, rising to peak faster and decaying away faster and had only a small post-overshoot. We then varied the length of time over which contrast increased or decreased. We used the positive and negative BOLD responses to estimate separate impulse response functions. These functions showed similar temporal differences for positive and negative responses. Furthermore, when we used these data to test for linear temporal summation we found that while positive responses show the well-known non-linearity whereby brief responses are larger than expected, the negative responses show an inverse pattern in which brief responses are smaller (i.e. less negative) than expected by linear summation. The difference between positive and negative responses are most likely not neural, but probably arise from differences in the linkage of metabolic activity to hemodynamics.

INTRODUCTION: The hemodynamic response in the brain is exquisitely specific to the place and time of increased metabolic activity. The advent of BOLD imaging which exploits this specificity to understand neural function has created great interest in understanding both the spatial precision and temporal dynamics of the BOLD response. While much progress has been made in characterizing the hemodynamic response for activations resulting from increased metabolic activity, there has been little investigation into the dynamics of deactivations resulting from decreased metabolic activity. In this study we examine the hemodynamic response for both activation and deactivations in the same voxels and test the predictions of linear temporal summation.

METHODS General: We studied the occipital visual cortex of six healthy subjects (five male and one female), two of which are authors (ages 27-39). All procedures were approved in advance by the RIKEN Functional MRI Safety and Ethics Committee and subjects gave prior written informed consent. Scans were conducted on a 4T whole-body MRI system with a Varian Unity Inova console using a quadrature surface coil. Head motion was restrained by a bite-bar system and heart rate, respiration and head motion were monitored. Stimuli were presented on fiber-optic goggles (800x600, 60 Hz) equipped with an infrared eye position monitor (Avotec Inc).

MRI parameters: We collected either two (high temporal resolution, data for Figure 1) or eight (low temporal resolution, data for Figure 2) four mm thick coronal slices perpendicular to the calcarine sulcus. Functional images were acquired with a two segment centric ordered EPI sequence which contained navigator echoes and required 100 ms per slice for a volume TR of either 0.2 (high temporal resolution) or 0.8 seconds (low temporal resolution) and a TE of 25 ms. High temporal resolution images had an in-plane resolution of 3.75 x 3.75 mm (FOV = 24x24 cm, matrix size = 64x64). Low temporal resolution images had a FOV of 20x20cm instead.

Task: We used an event-related paradigm to determine transient hemodynamic responses to increments and decrements of stimulus contrast. Imaging sessions began with 30 seconds of baseline measurements where a uniform gray screen was presented and subjects had to maintain fixation at a central cross. We then presented an 8 deg diameter 7.5Hz contrast-reversing checkerboard stimulus 5 deg from the fixation point in each visual quadrant at 25% contrast for 60 seconds. After this initial phase which allowed for neural adaptation to saturate, we presented brief (3 second) test contrasts that were two octaves above (100%) or below (6.25%) the initial contrast level. These test contrasts were presented in random order, interspersed with 28-32 seconds of baseline contrast. In a second set of experiments, we varied the length of the stimuli by using test contrasts that incremented (87.5%) or decremented (12.5%) by modulating from a baseline of 50% contrast following a half-cycle of a sinusoid of period 3.13, 4.17, 6.25, 8.33 and 12.5 seconds presented in separate experimental blocks. In these experiments, test contrast changes were interspersed with 8-12 seconds of baseline contrast. Subjects were required to maintain fixation throughout each imaging session during which at least 12 repeats of each test contrast was presented. Subject attention was controlled by asking subjects to report brief (1/30 sec) changes in the color of the fixation cross with a button press.

Data Analysis: Functional data was first preprocessed by removing physiological fluctuations due to heart rate and respiration via a retrospective correction, applying motion correction and filtering out low frequency signal drifts. We obtained unbiased estimates of hemodynamic response functions by standard methods (Dale 1999, Hum Brain Mapp, 8:109). We used the amount of variance accounted for by the estimated hemodynamic responses to identify activated voxels. We fit hemodynamic responses with a difference of gamma functions whose exponent. amplitude, tau and latency were adjusted to minimize the least squared error between the fit and the data. Visual areas were identified by reference to functional images acquired separately for each subject that defined the horizontal and vertical meridians.

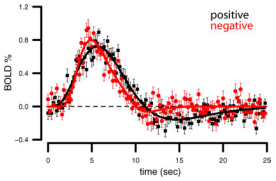

Figure 1. Average response in V1 to increases (black) and decreases (red) in stimulus contrast. The red curve is inverted for comparison with the black one.

RESULTS: Comparing the average response in V1 pooled over subjects which had peak amplitudes between ±0.4 – 1.2% BOLD, depicts the main effects that we found. The negative response, which has been inverted for comparison with the positive response (red curve, Figure 1) begins to rise slightly later, yet it reaches peak faster. After reaching peak it rapidly falls and shows very little post-undershoot. In a voxel-by-voxel comparison we fit gamma functions to the positive and negative responses in each voxel and compared parameters. On average, we found the lag to be longer for negative responses (1.77 vs 1.34 sec, $p<0.01$), the tau to be shorter (0.85 vs. 1.02 sec, $p<0.01$) and the rise to peak to be shorter (5.83 vs 6.20 sec, $p=0.09$). The trend towards differences in time-to-peak were found even for voxels with similar amplitude responses.

We then tested the temporal linearity of positive and negative response by conducting a linear systems analysis of data collected for contrast increments (Figure 2A) and decrements (Figure 2B) of different half sinusoidal periods averaged across subjects in V1. We calculated the hemodynamic impulse response function that when convolved with the stimulus for each duration best accounted for the observed BOLD response in a least squares sense. We did this separately for the positive (Figure 2C, black) and negative (Figure 2C, red) responses and found that the calculated impulse functions collected from these data showed similar differences in temporal dynamics as the data from Figure 1. Furthermore, when we used these impulse response functions to estimate the observed responses, we found that for positive responses there was a temporal non-linearity of the form observed by Boynton et al. (1996, J Neurosci:16:4207) in which brief responses were large (and consequently longer responses smaller) than expected by temporal linearity. In contrast, we found that for the negative responses, brief responses were smaller (i.e. less negative) and longer responses larger (i.e. more negative) than expected by linear summation.

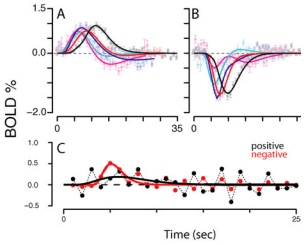

Figure 2. BOLD response to contrast increments (A) and decrements (B) of different lengths and predicted impulse response from these data (C).

DISCUSSION: Our results demonstrate that the BOLD response to increases and decreases in metabolic demand follow different time courses. The negative response has a longer delay, faster rise time and narrow width with very little "post-undershoot (overshoot)". Analyzing the response to stimuli of different lengths revealed the well-known violation of temporal linearity in which brief responses were larger than expected and conversely for negative responses we found that brief responses were smaller (i.e. less negative) than expected. The difference we have found are not expected from neurophysiological recordings of stimulus onset and offset (Bair et al. 2002, J Neurosci 22:3189) which show only differences in latency on the order of tens of ms—with onsets having a longer delay than offsets—an order of magnitude different from the dynamics we have found. We suggest that the differences we have documented between positive and negative responses arise from differences at the level of the transformation of metabolic demand to hemodynamic regulation.