Cortical Depth and Functional Duty Cycle Dependence of the Initial Dip and Post-stimulus Undershoot in Humans: A 7 Tesla BOLD Investigation.

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Introduction. The overall goal of this study was to investigate negative elements of the BOLD hemodynamic response function (HRF) as a function of cortical depth and stimulus duration by performing high spatial (1.35 mm in-plane) and temporal (TR=600 ms) BOLD fMRI in humans at 7.0T. Fundamentally, the BOLD HRF is comprised of (i) a transient reduction in signal (initial dip, ID), followed by (ii) a positive increase in signal, concluding with (iii) a signal reduction below baseline (post-stimulus undershoot, PSU). The positive BOLD response arises owing to an increase in oxygenation level in and around capillaries and veins, the extent of which may or may not be well-localized to tissue. Alternatively, the ID is hypothesized to arise from a faster increase in the cerebral metabolic rate of oxygen consumption ($CMRO_2$) relative to cerebral blood flow (CBF) [1], whereas the PSU has been debated to arise from delayed venular compliance, persisting elevated $CMRO_2$, and/or reduced CBF [2,3]. Importantly, negative HRF components may reflect more specific metabolic and/or hemodynamic properties than positive HRF components, possibly increasing specificity to activation. Owing to the spatial sensitivity of these features, the coarse spatial resolution (3-5 mm) and large intravascular BOLD contributions at 1.5T-3.0T largely precludes detailed spatial, mechanistic studies of these features. Furthermore, comparatively few 7.0T BOLD methodological studies focus on the ID and PSU [1], with the majority of studies addressing positive aspects of the HRF [4]. Therefore, it was the aim of this study to carefully measure spatial and temporal features of the ID and PSU as a function of cortical depth and stimulus duration at 7.0T. The hypotheses to be investigated were two-fold. First, owing to upstream propagation of vasodilation toward the cortical surface, the ID magnitude will be most pronounced in superficial cortical layers. Second, the BOLD PSU will be largest in deep cortical layers where capillary networks are densest. Results provide insight into the spatial and temporal characteristics of the ID and PSU, explanations for why these features are spuriously observed at lower field strength, and outline methods for sensitizing BOLD experiments to these phenomena.

Methods. *Experiment.* Volunteers (n=7) provided informed, written consent in accordance with the local ethics committee and were scanned at 7.0T (Philips) using a transmit head coil and 32-channel array receive coil. Third order image-based shimming was performed over visual cortex (**Fig. 1a**) and coronal, gradient echo EPI BOLD images (**Fig. 1b**; TR/TE=600/25 ms; 1.35x1.35x1.35 mm^3; 6 slices) were positioned over the visual cortex, as identified by a high resolution T_2*-weighted (T_2*w) localizer (**Fig. 1c**; TR/TE=105/20 ms; 0.5x0.5x0.5 mm^3). BOLD data were acquired for five different visual (blue/yellow 8 Hz flashing checkerboard) paradigms, each with separate stimulus duration (repetition blocks): 0.5s (16), 1s (8), 2s (5), 4s (5) and 8s (5), and all with constant inter-stimulus baseline period of 16s. *Analysis.* BOLD data were corrected for motion, baseline drift and co-registered to the T_2*w localizer using standard FSL algorithms [5]. To ensure robust activation, the FSL fMRI experimental analysis tool (FEAT) was used with gaussian-convolved boxcar regressor and general linear model (GLM) analysis (**Fig. 1d**; activation map criteria: Z>2.3; P<0.05). Measurements of cortical depth were made within a region of robust activation (**Fig. 1e,f**) and BOLD timecourses were calculated in five separate cortical regions (region thickness=0.6 mm). *Note, R1 denotes cortical surface and R5 the deepest region analyzed*. To prevent statistical bias, activation maps were not used for selecting voxels. The ROI was based instead on the cortical depth in regions with robust activation. ID and PSU duration and amplitude were calculated for each dataset.

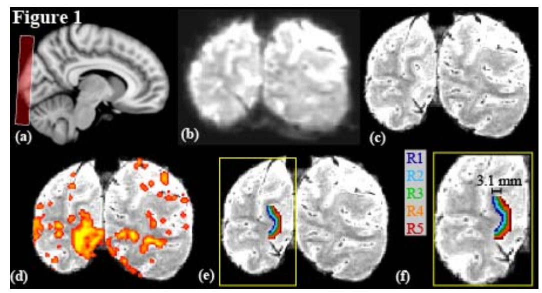

Fig. 1. Example (a) slice location, (b) 7.0T BOLD data, (c) T2*w image, (d) activation map, (e,f) cortical depth regions.

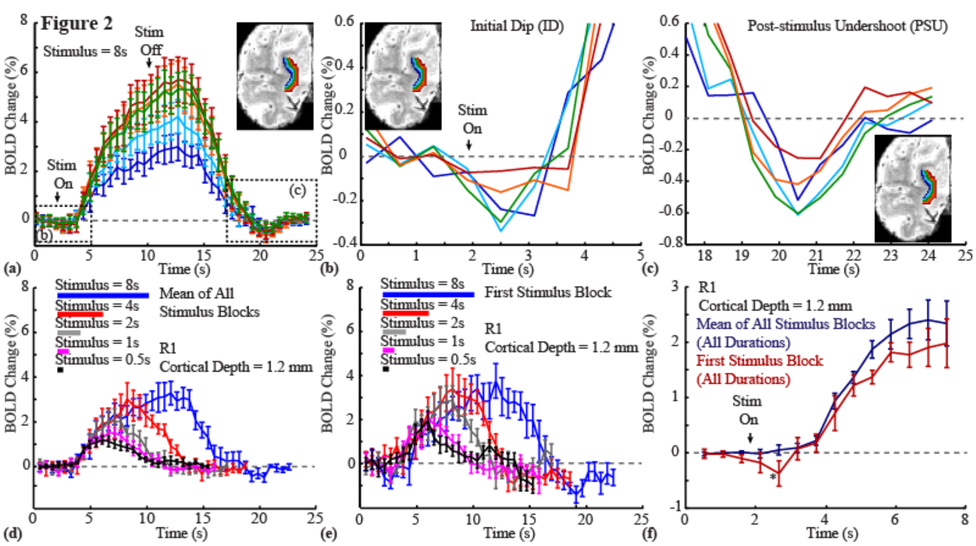

Fig. 2. (a) Stimulus=8s timecourses for all cortical regions, with magnification of (b) ID and (c) PSU. R1 timecourses for different stimulus durations (d) averaged over all stimulus blocks and (e) for the first block. (f) The ID is present for nearly all stimulus durations for the first block yet not for remaining blocks, with the exception of stimulus=8s (d), thus suggesting that the ID may be dependent on stimulus duty cycle.

Results and Discussion. Fig. 2 shows the 8s stimulus block-averaged response for all volunteers (**Fig. 2a**), with magnification of the ID (**Fig. 2b**) and PSU (**Fig. 2c**) periods shown separately. Note that the ID is largest and endures longest in peripheral regions (e.g. R1 and R2 relative to R4 and R5; P=0.048). The opposite trend was found for the PSU, with the PSU enduring longer (P=0.037) with slightly larger, but not significant (P=0.16), magnitude in deeper layers. **Fig. 2d,e** shows the total block-averaged HRF for R1 for different stimuli durations. **Fig. 2f** shows the difference in the ID when all blocks are averaged, versus only the first. These results demonstrate that the ID is cortically dependent, with the largest response occurring near the cortical surface. This finding is consistent with recent optical data in rats and attributed to upstream propagation of vasodilation toward the cortical surface, where the CBF/$CMRO_2$ mismatch is largest [6]. We show that this finding can similarly be observed in humans at 7.0T. Alternatively, the PSU endures longest in deep cortical layers, a finding that may be attributed to higher capillary density in this region, and better localization to $CMRO_2$ and CBF [7]. Surprisingly, the ID appears to exhibit a feature that is dependent on the functional duty cycle (**Fig. 2f**). For instance, there is relative consistency in the size and duration of the ID in the first stimulus block for all stimulus durations, yet a duration-dependent discrepancy between this block and the remaining blocks. Thus, block-averaging may not be desirable for fully characterizing ID dynamics in event-related paradigms. These findings may be attributable to neuronal adaptation and/or refractory phenomena [8].

References. [1] Yacoub E et al. NMR Biomed. 2001;14. **[2]** Buxton R, et al. MRM. 1998;39. **[3]** Lu H, et al. JCBFM. 2004;24. **[4]** Siero J, et al. JCBFM. 2011;31. **[5]** Jenkinson M, et al. Neuroimage. 2011;[E-pub]. **[6]** Tian P, et al. PNAS. 2010;107. **[7]** Harrison R, Cereb Cortex. 2002;12. **[8]** Birn R, et al. Neuroimage. 2005;27.