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Adaptation of cerebral oxygen metabolism and blood flow and modulation of neurovascular coupling with prolonged stimulation in human visual cortex

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Abstract

Prolonged visual stimulation results in neurophysiologic and hemodynamic adaptation. However, the hemodynamic adaptation appears to be small compared to neural adaptation. It is not clear how the cerebral metabolic rate of oxygen ($CMRO_2$) is affected by adaptation. We measured cerebral blood flow (CBF) and $CMRO_2$ change in responses to peripheral stimulation either continuously, or intermittently (on/off cycles). A linear system's response to the continuous input should be equal to the sum of the original response to the intermittent input and a version of that response shifted by half a cycle. The $CMRO_2$ response showed a large non-linearity consistent with adaptation, the CBF response adapted to a lesser degree, and the blood oxygenation level dependent (BOLD) response was nearly linear. The metabolic response was coupled with a larger flow in the continuous condition than in the intermittent condition. Our results suggest that contrast adaptation improves energy economy of visual processing. However BOLD modulations may not accurately represent the underlying metabolic nonlinearity due to modulation of the coupling of blood flow and oxygen metabolism changes.

1 Introduction

Prolonged exposure to a stimulus alters how subsequent stimuli are perceived. Adaptation is a form of neural plasticity that is ubiquitous in the sensory systems. Different forms of adaptation are present throughout the visual processing pathway (Clifford et al., 2007; Kohn, 2007). Adaptation may occur at different timescales (Bao & Engel, 2012; Patterson, Wissig, & Kohn, 2013). Intrinsic synaptic and neuronal mechanisms and extrinsic network interactions may be important for adaptation (Dhruv, Tailby, Sokol, & Lennie, 2011; Ghisovan, Nemri, Shumikhina, & Molotchnikoff, 2008; Sanchez-Vives, Nowak, & McCormick, 2000).

It has been suggested that adaptation optimizes neural coding efficiency (Adibi, McDonald, Clifford, & Arabzadeh, 2013; Attneave, 1954; Cortes et al., 2012; Gutnisky & Dragoi, 2008; Wark, Lundstrom, & Fairhall, 2007; Webster, 2011). Neural computations are energy intensive (Attwell & Iadecola, 2002; Howarth, Gleeson, & Attwell, 2012) and the structural

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and functional organization of the cortex are subject to metabolic constraints (Herculano-Houzel, 2011; Laughlin, 2001; Levy & Baxter, 1996). Adaptation may thus serve as a mechanism to reduce the metabolic cost of sensory processing and improve energy efficiency of neural computations.

Adaptation to the contrast of a visual stimulus occurs at multiple levels (Solomon, Peirce, Dhruv, & Lennie, 2004) and affects responses of the majority of neurons in early visual areas (Crowder et al., 2006). Adaptation to contrast has been demonstrated in human visual cortex using BOLD fMRI (Gardner et al., 2005), although in several instances BOLD fMRI has failed to reveal the underlying neural adaptation in primary visual cortex (Boynton & Finney, 2003; Murray, Olman, & Kersten, 2006; Weigelt, Limbach, Singer, & Kohler, 2012). However, the interpretation of BOLD adaptation is complicated by the complex nature of the BOLD response. Because the BOLD response depends on the combined changes in cerebral blood flow (CBF) and cerebral metabolic rate of oxygen ($CMRO_2$), BOLD adaptation necessarily involves a combination of CBF and $CMRO_2$ adaptation. While we expect the $CMRO_2$ adaptation to follow the neural adaptation, CBF adaptation may not. The steady-state relationship between BOLD and $CMRO_2$ modulation is predominantly determined by the neurovascular coupling ratio (n=ΔCBF/Δ$CMRO_2$). Both bottom up and top-down inputs to early sensory areas can affect the coupling between metabolic and hemodynamic activity (Liang et al., 2013; Moradi, Buračas, & Buxton, 2012). Even when such effects are minimized, BOLD-fMRI could misrepresent metabolic adaptation if neurovascular-coupling changes with prolonged stimulation.

Interpretation of BOLD adaptation is further complicated by dynamic aspects of hemodynamic signals underlying BOLD modulations (Richard B Buxton, 2010, 2012). Hemodynamic responses are nonlinear for very short stimulus durations (Gu, Stein, & Yang, 2005; Uludağ et al., 2004; Yeşilyurt, Uğurbil, & Uludağ, 2008), possibly reflecting transient dynamics of cerebral blood flow and volume changes in cerebral cortex (Birn & Bandettini, 2005; Z. Liu et al., 2010). To minimize transient hemodynamic nonlinearity it is imperative to examine adaptation on a time scale that is longer than the cerebral arteriovenous transit time.

We examined adaptation of CBF, $CMRO_2$ and neurovascular coupling to prolonged stimulation using combined CBF and BOLD measurements while subjects were exposed to peripheral continuous or intermittent flickering gratings. In both conditions the visual system adapts to a fixed contrast level and adaptation builds up over time (Greenlee, Georgeson, Magnussen, & Harris, 1991). In the intermittent condition, the stimulation epochs are interleaved with blank periods allowing partial recovery from adaptation whereas the continuous condition maximizes adaptation. The intermittent condition was used to predict the response to the continuous condition. The difference between predicted and observed response to the continuous stimulus was then attributed to the effect of adaptation. That is, adaptation is operationally defined for each metric (BOLD, CBF, and $CMRO_2$) as the difference between predicted and observed response to the continuous stimulus. Of these three measures, $CMRO_2$ adaptation likely represents adaptation of evoked neural activity response to the stimulus (assuming a tight coupling between neural processing and oxidative metabolism (Hall, Klein-Flüge, Howarth, & Attwell, 2012)), whereas CBF adaptation likely represents a combination of hemodynamic non-linearity and adaptation of the mechanism by which neural signals drive blood flow (Attwell & Iadecola, 2002). The balance between $CMRO_2$ and CBF adaptation would determine BOLD adaptation and how well it reflects adaptation of neural activity (i.e., $CMRO_2$ adaptation).

Two different contrast levels were tested. High contrast stimulation increases signal to noise. However, the neural and/or hemodynamic response may saturate at high magnitudes of activity. Therefore low contrast stimulation was included for comparison.

Our primary finding was that contrast adaptation was stronger for $CMRO_2$ than CBF, with the combined effects producing minimal net BOLD adaptation. These data suggest that the BOLD signal alone is only weakly sensitive to neural adaptation, despite a pronounced adaptation of $CMRO_2$.

2 Methods

2.1 Participants

The institutional review board at the University of California San Diego approved the experimental protocol. After obtaining written informed consent six volunteers (age 27–37, two females, all subjects naïve except FM) participated in the experiment.

2.2 Scan Parameters

A multi-pulse pseudo-continuous arterial spin labeling sequence (Shin, Liu, Wong, Shankaranarayanan, & Jung, 2012) (Optimized-MP PCASL, TR=3.5 s, 1600 ms tag duration at the level of internal carotid and vertebral arteries, 1400 ms post labeling delay) with a dual-echo gradient echo (GRE) spiral readout (TE1=3.2 ms, TE2=32ms, flip angle 90°, FOV 24 cm, matrix 64 × 64, eight 7-mm slices with 0.5 mm gap centered around the Calcarine sulcus) was used to simultaneously acquire cerebral blood flow (CBF) and BOLD responses in a 3 Tesla GE Signa Excite 3T whole body MRI scanner using the body coil for transmission and an 8-channel head coil receiver.

2.3 Stimuli and Task

Participants fixated at the center of the display and were presented with peripheral grating stimuli using a block design paradigm. A cognitively engaging fixation task (unrelated to the peripheral stimuli of interest) was used to control attention and eye-movements.

The display (1024×768@60 Hz, approximately 22°×16° visual angle via back projection) comprised a small red central fixation point (0.15°) over mid-gray background. Black digits (0.6°) appeared superimposed on fixation at 2 Hz (300 ms on, 200 ms off) in a pseudorandom order. Participants were instructed to fixate at the center of the screen and perform a one-back memory task on digits appearing at fixation to control attention during the whole run.

Peripheral stimuli (checkerboards flickering at 3 Hz, 10% or 80% of the maximal display contrast, subtending 1–10° eccentricity) were presented either continuously for 45.5 s (13 TRs), or intermittently as three epochs of 7.583 s on and off duration (Figure 1). Participants were instructed to ignore the peripheral stimuli. Each stimulation epoch was followed by 56 s blank period.

Each subject performed four low-contrast and 2–4 high-contrast runs. The initial 14 s (4 TR) of each run was discarded. Baseline (no peripheral stimulation) was acquired for 49 s at the beginning (head) and end of each run (tail). Each run comprised two continuous and two intermittent blocks (Figure 1), with the order of presentation counterbalanced across runs.

The stimuli were presented using Matlab psychophysics toolbox (Brainard, 1997).

2.4 Analysis

The blurring of spiral images caused by field inhomogeneities was corrected based on an iterative algorithm (Sutton, Noll, & Fessler, 2003). Functional images were coregistered and corrected for subject motion during and between scans using AFNI (Cox, 1996). Physiological noise correction was performed using cardiac and respiratory data collected during the scan with a method based on RETROICOR (Glover, Li, & Ress, 2000; Restom, Behzadi, & Liu, 2006). The first four TRs (14 s) of each run were discarded. *BOLD* and *CBF* were calculated from the second and first echo, respectively, using the surround subtraction method (T. T. Liu & Wong, 2005). The data was analyzed in Matlab using in-house developed software (Behzadi, 2006).

Activation maps were generated from the corrected data using a general linear model (GLM). A region of interest (ROI) was defined from the intersection of active voxels for both BOLD and flow maps for each subject (thresholded at $p<0.05$). Isolated clusters smaller than 3 voxels were excluded. Activity time courses were obtained by averaging BOLD and flow across all voxels within the ROI. Time courses were then normalized by dividing by the temporal average of the initial (head) and final 49 s (tail) of each run. This ROI-based analysis was used because voxel-wise normalization is impractical for flow data due to low signal within a voxel relative to thermal noise. Both BOLD and flow data were processed in a similar fashion.

Evidence for adaptation was examined in two related ways. First, the net magnitude of a response (BOLD or CBF) was taken as the mean value of that parameter during a window from one to 13 TRs (3.5 – 45.5 s) after onset of the stimulation for each condition (intermittent versus continuous) and contrast level (low versus high) for each subject. Shifting the integration window by ±1 TR did not affect our conclusions. This window included the full response to each set of stimuli, and for a simple linear response the net magnitude for the continuous response would be expected to be 100% larger than the net magnitude for the intermittent response because the stimulus is on for only half of the interval in the intermittent stimulus. A value of this ratio less than 100% is a sign of adaptation effects. Second, the intermittent response was shifted by half a cycle and added to the original response to produce a linear prediction for the continuous response. A measured response to the continuous stimulus that is less than the predicted response calculated from the intermittent stimulus also is taken as a sign of adaptation effects.

2.5 $CMRO_2$ estimation

A modified Davis model (Davis, Kwong, Weisskoff, & Rosen, 1998; Griffeth & Buxton, 2011) was used to estimate the metabolic response.

$$\Delta b = M\left(1 - f^{\alpha-\beta} r^{\beta}\right)$$

Where b, f, and r represent normalized BOLD, flow, and $CMRO_2$, M is a scaling parameter, and alpha and beta are constants ($\alpha = 0.16$, $\beta = 1$ based on (Griffeth & Buxton, 2011)). The scaling parameter was estimated for each subject from the data by assuming a fixed neurovascular-coupling ratio for all subjects for the high contrast continuous condition (n_{HC}).

$$M=\frac{b_{HC}-1}{1-f_{HC}^{\alpha-\beta}r_{HC}^{\beta}}$$

where f_{HC} and b_{HC} denote the normalized cerebral blood flow and BOLD response in the high contrast continuous condition, and $r_{HC} = 1 + (f_{HC} - 1)/n_{HC}$. The assumed high contrast neurovascular-coupling ratio was varied from 1.4 to 30 (Results are shown for n_{HC}=2.5). The estimated metabolic responses are

$$r=f^{0.84}\left(1-\frac{b-1}{M}\right)$$

2.6 Adaptation index

Adaptation index was quantified as the difference of non-adapted (intermittent response) and adapted (continuous response) divided by the average response of the two conditions. An adaptation index of zero implies linearity: doubling the duration of stimulation would double the evoked response integrated over time. A positive adaptation index implies a sub-linear response, whereas a negative adaptation index implies a super-linear response. If the response reaches its maximum with intermittent stimulation, the adaptation index would be one.

2.7 BOLD simulation

The complex dynamics of the BOLD signal and its dependence on the cerebral blood volume (CBV) change could result in additional temporal non-linearities. To examine dynamic CBV effects we simulated BOLD response in the absence of flow and $CMRO_2$ adaptation using a detailed biophysical BOLD model (Griffeth & Buxton, 2011). A compliant balloon model (R B Buxton, Wong, & Frank, 1998) was used to calculate dynamic volume changes in arterioles, capillaries, and venules. Simulations were performed with different assumptions about the magnitude and rate of volume change in each vascular compartment. Specifically, volume dynamics was assumed to be in the form of

$$\tau\frac{dv}{dt}=f-v^{1/\alpha}$$

Volume normalized to its baseline value is denoted by v, α is the Grubb's constant, and τ denotes the viscoelastic time constant (2 s for artery, either 3 s or 30 s for vein). To simulate CBV change that is predominantly arterial (venous), α was set to 0.7 (0.12) for arterial, 0.1 (0.1) for capillary, and 0.2 (0.5) for venous compartment. Normalized flow and metabolic response were set to 0.1 and 0.04 (giving a neurovascular coupling ratio of 2.5).

3 Results

The BOLD and flow signals in the region of interest in the occipital cortex were modulated with stimulation (Figure 2). Both signals rise quickly after stimulus onset (a positive signal is evident in the first TR), returning rapidly to baseline (or below baseline) following stimulus offset. A post-stimulus BOLD undershoot is observed although a flow undershoot is not clearly present in every condition.

The modulation of BOLD and CBF is larger with continuous stimulation than with intermittent stimulation and increases with stimulus contrast ($F_{3,15}$=29.6 for flow, $F_{3,15}$=40.1 for BOLD, Tukey-Kramer post-hoc test p=0.06 for BOLD response to intermittent low versus high contrast stimulation, p<0.05 for all other comparisons).

The input function in the continuous condition (Figure 1) is by construction equal to the sum of the input function for the intermittent condition and a version of that input function shifted by 7.583 s. Consequently, a linear system's response to the continuous input would be equal to the sum of the original response to the intermittent input and a version of that response shifted by 7.583 s. The linear model predictions (gray) and observed modulations (thick black line) are compared in Figure 2.

The flow modulations behave in a sub-linear fashion: the average observed flow modulation evoked by continuous stimulation (thick black curve) is less than the predicted linear-model response for both low and high-contrast stimuli. Continuous stimulation increases the net average flow response during the stimulation window compared to the intermittent condition by 51% for both low and high contrast stimuli (20.2 vs. 13.4 and 29 vs. 19.2 percent signal change averaged across participants, respectively; Figure 4).

In comparison, continuous stimulation increases the net average BOLD response by 94% for low- and 96% for high-contrast stimuli (0.94 vs. 0.48 and 1.44 vs. 0.74 percent signal change, respectively). The observed and predicted BOLD modulations match closely. There is a suggestion of a small deviation from linearity in the first 25 s of the BOLD response with high contrast stimuli followed by an opposite and apparently larger effect in the next 20–25 s. A possible small deviation from linearity during the post-stimulus undershoot is noted. However, these effects are not invariably present across observers.

An *adaptation index* (AI) was calculated for each subject, defined as the difference between the predicted and observed response normalized by the average of the two. Figure 3 compares adaptation indices for BOLD, flow, and oxygen metabolism ($CMRO_2$). Flow demonstrates significant adaptation for both low- (AI = 0.25±0.09) and high-contrast stimuli (AI = 0.26+0.12, mean ± standard deviation) (two-tailed t-test t_5>5.4, p<0.01 for both conditions). BOLD adaptation is not significantly different from zero (t_5=−0.79, p=0.47 for low contrast, t_5= −0.49, p=0.64 for high contrast).

We conducted quantitative analysis of BOLD and flow data and estimated $CMRO_2$ modulation. Assuming a n_{HC} of 2.5 for the high contrast continuous stimulation, modulation of $CMRO_2$ activity is significantly larger with high contrast stimulation than with low contrast stimulation and with continuous stimulation than with intermittent stimulation ($F_{3,15}$=10.98 p<0.001, post-hoc p<0.05 for all comparisons). $CMRO_2$ adaptation is significant for both low- (AI = 0.45±0.09) and high-contrast stimuli (AI = 0.54±0.05). The adaptation index for oxygen metabolism was greater than for flow ($F_{3,15}$=13.32, p<0.001, post-hoc p<0.05 for both low- and high-contrast, Figure 3). The adaptation index did not depend on stimulus contrast.

Similar results were obtained when different values of n_{HC} were tested (range = 1.4 – 30). $CMRO_2$ adaptation was significant for both low-contrast (p≤0.0003, two-tailed t-tests) and high contrast (p≤0.0003) stimuli and was greater than adaptation of flow regardless of n_{HC} (p≤0.002 for low-contrast, p≤0.012 for high contrast). Prolonged stimulation modulated the neurovascular coupling parameter n (p≤ 0.03 low-contrast, p≤0.009 high-contrast). Contrast level also modulated the neurovascular coupling parameter, similar to a previous study (Liang et al., 2013), although this was significant consistently only for the continuous stimulation (p≤0.016).

We verified that our results are not statistically biased by the choice of ROI (Poldrack, 2006). The high contrast data were reanalyzed using an ROI defined independently based on the low contrast runs. There was significant adaptation of flow (p<0.01) and $CMRO_2$ (p≤0.0006 for n_{HC}=1.4 – 30), but not BOLD (p>0.6). $CMRO_2$ adaptation was greater than flow adaptation (p≤ 0.017) for all values of n_{HC} tested.

To examine whether the choice of model used to estimate metabolic response alters our analysis we reanalyzed our data using the original Davis model (Davis et al., 1998), and two other models with different assumptions about the form of BOLD non-linearity (Obata et al., 2004; Sanganahalli, Herman, Blumenfeld, & Hyder, 2009) (See Moradi et al., 2012 Supplementary Material for details). In all models, $CMRO_2$ adaptation was significant for both high and low contrast regardless of the assumed value of n_{HC}. One of the models (Obata et al., 2004) was not compatible with n_{HC} <2.04 (resulting in a negative BOLD scaling parameter), and for this model the difference between flow and $CMRO_2$ adaptation was marginally significant for n_{HC} =2.04 and high-contrast stimulus (p=0.0502) and was significant (p<0.05) for low contrast stimulus and/or n_{HC} = 2.05 – 30. $CMRO_2$ adaptation was significantly greater than flow adaptation in all other models regardless of n_{HC} (range = 1.4 – 30).

A potential confounding effect in these estimates of $CMRO_2$ change is the possibility of different venous CBV changes for the continuous and intermittent stimuli. To gain insight about the potential effect of dynamic changes in venous blood volume we simulated our experiment using a detailed biophysical model of BOLD signal with different assumptions about the magnitude and rate of blood volume changes (Figure 5). While venous CBV changes add dynamic features to the response, depending on the magnitude and time constant of the CBV changes, these features do not produce significant BOLD temporal non-linearity that would lead to a mis-identification of adaptation.

4 Discussion

4.1 Adaptation of flow and $CMRO_2$

In this experiment the BOLD and CBF responses to a continuous stimulus and an intermittent stimulus covering the same total duration were compared to test for adaptation effects in human visual cortex. Because the intermittent stimulus is on for only half of the net duration, a purely linear response (i.e., with no adaptation effects) is expected to increase by 100% in the continuous condition compared to the intermittent condition. An increase of less than 100% was taken as evidence of adaptation. Continuous stimulation increased the net flow response compared to the intermittent condition by approximately 51% for both low and high contrast stimuli, consistent with significant effects of adaptation. In contrast, the corresponding BOLD response ratio was 94% and 96% for the low- and high-contrast stimuli, suggesting little effect of adaptation (these numbers were not significantly different from 100%, the expected value in the absence of adaptation).

Because the BOLD response depends on the combined changes in flow and oxygen metabolism, this divergence of the CBF and BOLD responses in terms of adaptation effects is likely due to adaptation effects on the $CMRO_2$ response. The combined CBF and BOLD data were used to estimate the underlying adaptation of $CMRO_2$ using current models of the BOLD effect. Quantitative analysis of our data reveals that the adaptation effects for the $CMRO_2$ response are even greater than for the CBF response. The $CMRO_2$ response reflects the overall energy costs of the underlying neural activity change, and so is likely to be a better indicator of neural adaptation than either the BOLD or CBF response. The exact magnitude of adaptation depends on the analysis model and assumptions about the CBF/$CMRO_2$ coupling ratio n_{HC}. However, the degree of adaptation for $CMRO_2$ is larger than

flow adaptation for all models tested. Adaptation of BOLD, flow, and $CMRO_2$ are compared in figure 3 for n_{HC} =2.5.

A disproportionately larger adaptation of oxygen metabolism compared to flow adaptation explains the discrepancy between flow and BOLD adaptation, as shown by these calculations. Flow and $CMRO_2$ changes have opposite effects on the BOLD signal, and the BOLD response depends strongly on the flow/metabolism ratio. In this case the adaptation of the CBF response alone would have created an adaptation effect in the BOLD response if the $CMRO_2$ response adapted to the same degree. However, because the adaptation of $CMRO_2$ was more pronounced, the BOLD response in the adapted condition was increased, counteracting the effect on the BOLD response due to CBF adaptation alone. For the observed flow/metabolism ratios, differential flow and $CMRO_2$ adaptation effects cancel, producing little net adaptation of the BOLD response for both low and high contrast stimuli. Our results may explain prior studies failing to demonstrate BOLD adaptation in the primary visual cortex (Boynton, Engel, Glover, & Heeger, 1996; Boynton & Finney, 2003).

4.2 Time-scale of hemodynamic non-linearity

BOLD non-linearity has been demonstrated at short timescales (Miller et al., 2001; Pfeuffer, McCullough, Van de Moortele, Ugurbil, & Hu, 2003; Vazquez & Noll, 1998; Wager, Vazquez, Hernandez, & Noll, 2005). Transient hemodynamic effects may contribute to such a non-linearity (Friston, Josephs, Rees, & Turner, 1998; Friston, Mechelli, Turner, & Price, 2000; Gu et al., 2005). Using stimulation durations (7.58 s in intermittent condition) that are longer than the blood transit time in cortex (approximately 4 s) we tried to minimize the interplay between changes in volume of different blood compartments and changes in oxygenation of flowing blood.

4.3 $CMRO_2$ estimation

$CMRO_2$ modulations can be estimated from the BOLD and CBF data using a calibrated technique (Nicholas P Blockley, Griffeth, & Buxton, 2012; Davis et al., 1998) by performing additional scans typically using hypercapnia and measuring the BOLD scaling parameter. This approach assumes that the neurovascular coupling for hypercapnic changes is known, usually assuming no modulation of metabolism in hypercapnia. More generally, if the neurovascular coupling for one of the conditions is known, the $CMRO_2$ responses to other conditions can be calculated. Here, we assume that the neurovascular coupling for high contrast continuous stimulation (n_{HC}, see methods) is known and is the same for all subjects. The advantage of this approach is that a separate calibration is not needed. Neurovascular coupling has better reproducibility and similar inter-observer variability compared to the BOLD scaling factor (Leontiev & Buxton, 2007). Since the results might depend on the initial assumption of n_{HC} we validated our conclusions for a wide range of n_{HC}. We also validated our findings using other metabolic response models (Davis et al., 1998; Obata et al., 2004; Sanganahalli et al., 2009).

Accurate estimation of $CMRO_2$ requires accounting for the effect of cerebral blood volume (CBV) on BOLD signal. Slow change in the venous fraction of CBV has been reported with prolonged stimulation (Kim & Kim, 2011) but not with short stimulation (Kim, Hendrich, Masamoto, & Kim, 2007). Increased venous CBV is thought to represent passive dilation of high compliance venules driven by increased blood flow (R B Buxton et al., 1998; Mandeville et al., 1999). In the intermittent condition the blank interval between stimulations is short compared to the time needed for CBV to return to baseline (N P Blockley, Francis, & Gowland, 2009), therefore we expect a slow CBV response to build up with multiple stimulations in a similar fashion to CBV modulation with prolonged continuous stimulation. Simulations using a balloon model demonstrate that the effect of

CBV changes on BOLD response in the intermittent and continuous conditions are proportional to flow changes regardless of the time constant of volume change (Figure 5). Therefore errors in calculation of CBV due to slow volume change would likely not affect the adaptation index. Even if the venous CBV change in the continuous condition is disproportionally large compared to the intermittent condition, the actual $CMRO_2$ response to continuous stimulus would be smaller than our estimate and therefore $CMRO_2$ adaptation would be even larger, strengthening our conclusions.

4.4 Modulation of neurovascular coupling

A notable aspect of our result is that prolonged stimulation increased the neurovascular coupling ratio n compared to intermittent stimulation (Figure 4). We had previously shown that n is affected by stimulus contrast (Liang et al., 2013) and top-down effects related to attention (Moradi et al., 2012). Our results are consistent with the hypothesis that blood flow is driven in visual cortex by both metabolic activity and feed-forward input from neural activity. In the continuous condition the metabolic response is reduced due to adaptation, but the flow is still driven by continuous retinal input, resulting in a large n. Adaptive modulation of neurovascular coupling suggests that a linear relationship between hemodynamic signals and neural activity is not always the case. Our findings point to distinct aspects of metabolism that are coupled differently to blood flow. The observed changes in blood flow are the cumulative effect of different underlying hyperemic responses. If the relative contribution of these hyperemic responses remain the same (or if they change in a way that cancel out the effect of each other) a linear relationship between the average neural activity within a cortical region and hemodynamic activity (Heeger, Huk, Geisler, & Albrecht, 2000; Hyder et al., 2010; Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001) will be observed.

4.5 Effect of region of interest

One of the limitations of our study is that we did not separate responses in different visual areas. Lack of adaptation of BOLD signal may indicate a relatively large contribution of signal originating in V1 compared to other areas that demonstrate BOLD adaptation (Boynton & Finney, 2003). It is possible that the subset of the ROI that adapts the most to prolonged stimulations could have a lower n than the rest of the visual cortex. Large voxel size, low ASL signal to noise, and low-frequency drifts in BOLD signal limit our ability to examine differences between distinct subpopulations of neurons that may be otherwise resolvable using conventional or high-resolution BOLD fMRI.

4.6 Relationship between neural and fMRI adaptation

Contrast adaptation is best demonstrated both psychophysically and in single cell recordings using high contrast stimuli for adaptation and low contrast stimuli for testing (Albrecht, Farrar, & Hamilton, 1984; Sclar, Lennie, & DePriest, 1989). It is more difficult to temporally separate response to adapting and test stimuli in fMRI than in electrophysiology. We used the same contrast for both adaptation and test, similar to repetition suppression paradigms (Grill-Spector & Malach, 2001; Larsson & Smith, 2012). Doing so enabled us to simplify the analysis, eliminating the need to explicitly separate the responses. However, our paradigm might elicit a combination of heterogeneous neuronal adaptation effects (Weigelt, Muckli, & Kohler, 2008), and our results might not directly correlate to prior electrophysiological studies of specific forms of adaptation. Top-down attention may confound activity evoked by repeating the stimulus (Henson & Mouchlianitis, 2007; Larsson & Smith, 2012; Yi, Kelley, Marois, & Chun, 2006), which was minimized by instructing observers to divert attention from peripheral stimuli and engaging them in a cognitively demanding central fixation task.

4.7 BOLD nonlinearity

Generally BOLD is a non-linear function of increasing blood flow with a finite ceiling (Griffeth & Buxton, 2011; Simon, Griffeth, Wong, & Buxton, 2013). For a small change from baseline, the relationship between BOLD and flow is approximately linear. Continuous stimulation increases flow response compared to the intermittent condition by approximately 51%. Therefore, the BOLD response is expected to increase at most by 51% (if the response is small and not approaching the ceiling). As a corollary, the relative BOLD response increase is expected to be larger for the low-contrast stimulus than for the high contrast stimulus because the response to high contrast stimulus is closer to the BOLD response ceiling. However, the BOLD response increased 94% for low- and 96% for high-contrast stimuli, near the value of 100% corresponding to no adaptation. That is, BOLD adaptation is considerably less than expected from underlying blood flow changes.

Our results should not be interpreted as evidence of linearity or additivity of the BOLD response. BOLD non-linearity may occur at timescales different from what is measured using the adaptation index. We did not try to optimize our paradigm or analysis to maximize BOLD adaptation and our sample size is relatively small, thus our ability to resolve a small BOLD non-linearity is limited. Interestingly, BOLD responses decrease over time in all conditions (Figure 2). This negative trend may be construed as adaptation. However, both continuous and intermittent conditions demonstrate very similar trends, suggesting that the mechanism underlying decreased BOLD response over time does not appreciably recover in the 7.58s inter-stimulus intervals. Moreover, since the flow responses show a noticeably smaller change over time, if the decrease in BOLD signal is attributed to a change in metabolism it should imply an increase in $CMRO_2$ over time in all conditions (opposite of adaptation). Our results illustrate how BOLD fMRI could underestimate or overestimate the underlying metabolic adaptation.

5 Conclusion

Visual adaptation improves efficiency of visual processing not only in terms of improving coding efficiency and removing redundancy, but also decreases the metabolic cost and improves energy economy of neural computations. As a result of adaptation, the sensory system becomes more sensitive to subsequent changes in inputs. Our results suggest that the visual system may also adapt to preserve metabolic resources for subsequent processing. Importantly, our results also show that adaptation of the BOLD response significantly underestimates the underlying adaptation effects on blood flow and oxygen metabolism. Quantitative fMRI methods, focusing on determination of the $CMRO_2$ response, provide an fMRI window that is a step closer to neural activity, and in this study led to a different conclusion about neural adaptation than what was indicated by the BOLD data alone.

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References

Adibi M, McDonald JS, Clifford CWG, Arabzadeh E. Adaptation improves neural coding efficiency despite increasing correlations in variability. The Journal of neuroscience: the official journal of the Society for Neuroscience. 2013; 33(5):2108–2120.10.1523/JNEUROSCI.3449-12.2013 [PubMed: 23365247]

Albrecht DG, Farrar SB, Hamilton DB. Spatial contrast adaptation characteristics of neurones recorded in the cat's visual cortex. The Journal of physiology. 1984; 347:713–739. [PubMed: 6707974]

Attneave F. Some informational aspects of visual perception. Psychological review. 1954; 61(3):183–193. [PubMed: 13167245]

Attwell D, Iadecola C. The neural basis of functional brain imaging signals. Trends in Neurosciences. 2002; 25(12):621–625. [PubMed: 12446129]

Bao M, Engel SA. Distinct mechanism for long-term contrast adaptation. Proceedings of the National Academy of Sciences of the United States of America. 2012; 109(15):5898–5903.10.1073/pnas.1113503109 [PubMed: 22454502]

Behzadi, Y. Variability in functional magnetic resonance imaging: influence of the baseline vascular state and physiological fluctuations. Univeristy of California; San Diego: 2006.

Birn RM, Bandettini PA. The effect of stimulus duty cycle and "off" duration on BOLD response linearity. NeuroImage. 2005; 27(1):70–82.10.1016/j.neuroimage.2005.03.040 [PubMed: 15914032]

Blockley NP, Francis ST, Gowland PA. Perturbation of the BOLD response by a contrast agent and interpretation through a modified balloon model. NeuroImage. 2009; 48(1):84–93.10.1016/j.neuroimage.2009.06.038 [PubMed: 19559799]

Blockley, Nicholas P.; Griffeth, VEM.; Buxton, RB. A general analysis of calibrated BOLD methodology for measuring CMRO2 responses: comparison of a new approach with existing methods. NeuroImage. 2012; 60(1):279–289.10.1016/j.neuroimage.2011.11.081 [PubMed: 22155329]

Boynton GM, Engel SA, Glover GH, Heeger DJ. Linear Systems Analysis of Functional Magnetic Resonance Imaging in Human V1. The Journal of Neuroscience. 1996; 16(13):4207–4221. [PubMed: 8753882]

Boynton GM, Finney EM. Orientation-specific adaptation in human visual cortex. The Journal of neuroscience: the official journal of the Society for Neuroscience. 2003; 23(25):8781–8787. [PubMed: 14507978]

Brainard DH. The Psychophysics Toolbox. Spatial vision. 1997; 10(4):433–436. [PubMed: 9176952]

Buxton RB, Wong EC, Frank LR. Dynamics of blood flow and oxygenation changes during brain activation: the balloon model. Magnetic resonance in medicine: official journal of the Society of Magnetic Resonance in Medicine/Society of Magnetic Resonance in Medicine. 1998; 39(6):855–864. [PubMed: 9621908]

Buxton, Richard B. Interpreting oxygenation-based neuroimaging signals: the importance and the challenge of understanding brain oxygen metabolism. Frontiers in Neuroenergetics. 2010; 2:8.10.3389/fnene.2010.00008 [PubMed: 20616882]

Buxton, Richard B. Dynamic models of BOLD contrast. NeuroImage. 2012; 62(2):953–961.10.1016/j.neuroimage.2012.01.012 [PubMed: 22245339]

Clifford CWG, Webster MA, Stanley GB, Stocker AA, Kohn A, Sharpee TO, Schwartz O. Visual adaptation: neural, psychological and computational aspects. Vision research. 2007; 47(25):3125–3131.10.1016/j.visres.2007.08.023 [PubMed: 17936871]

Cortes JM, Marinazzo D, Series P, Oram MW, Sejnowski TJ, Van Rossum MCW. The effect of neural adaptation on population coding accuracy. Journal of computational neuroscience. 2012; 32(3):387–402.10.1007/s10827-011-0358-4 [PubMed: 21915690]

Cox RW. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. Computers and Biomedical Research, an International Journal. 1996; 29(3):162–173.

Crowder NA, Price NSC, Hietanen MA, Dreher B, Clifford CWG, Ibbotson MR. Relationship between contrast adaptation and orientation tuning in V1 and V2 of cat visual cortex. Journal of neurophysiology. 2006; 95(1):271–283.10.1152/jn.00871.2005 [PubMed: 16192327]

Davis TL, Kwong KK, Weisskoff RM, Rosen BR. Calibrated functional MRI: mapping the dynamics of oxidative metabolism. Proceedings of the National Academy of Sciences of the United States of America. 1998; 95(4):1834–1839. [PubMed: 9465103]

Dhruv NT, Tailby C, Sokol SH, Lennie P. Multiple adaptable mechanisms early in the primate visual pathway. The Journal of neuroscience: the official journal of the Society for Neuroscience. 2011; 31(42):15016–15025.10.1523/JNEUROSCI.0890-11.2011 [PubMed: 22016535]

Friston KJ, Josephs O, Rees G, Turner R. Nonlinear event-related responses in fMRI. Magnetic resonance in medicine: official journal of the Society of Magnetic Resonance in Medicine/Society of Magnetic Resonance in Medicine. 1998; 39(1):41–52. [PubMed: 9438436]

Friston KJ, Mechelli A, Turner R, Price CJ. Nonlinear responses in fMRI: the Balloon model, Volterra kernels, and other hemodynamics. NeuroImage. 2000; 12(4):466–477.10.1006/nimg.2000.0630 [PubMed: 10988040]

Gardner JL, Sun P, Waggoner RA, Ueno K, Tanaka K, Cheng K. Contrast adaptation and representation in human early visual cortex. Neuron. 2005; 47(4):607–620.10.1016/j.neuron.2005.07.016 [PubMed: 16102542]

Ghisovan N, Nemri A, Shumikhina S, Molotchnikoff S. Synchrony between orientation-selective neurons is modulated during adaptation-induced plasticity in cat visual cortex. BMC neuroscience. 2008; 9:60.10.1186/1471-2202-9-60 [PubMed: 18598368]

Glover GH, Li TQ, Ress D. Image-based method for retrospective correction of physiological motion effects in fMRI: RETROICOR. Magnetic Resonance in Medicine: Official Journal of the Society of Magnetic Resonance in Medicine/Society of Magnetic Resonance in Medicine. 2000; 44(1): 162–167. [PubMed: 10893535]

Greenlee MW, Georgeson MA, Magnussen S, Harris JP. The time course of adaptation to spatial contrast. Vision research. 1991; 31(2):223–236. [PubMed: 2017883]

Griffeth VEM, Buxton RB. A theoretical framework for estimating cerebral oxygen metabolism changes using the calibrated-BOLD method: modeling the effects of blood volume distribution, hematocrit, oxygen extraction fraction, and tissue signal properties on the BOLD signal. NeuroImage. 2011; 58(1):198–212.10.1016/j.neuroimage.2011.05.077 [PubMed: 21669292]

Grill-Spector K, Malach R. fMR-adaptation: a tool for studying the functional properties of human cortical neurons. Acta Psychologica. 2001; 107(1–3):293–321. [PubMed: 11388140]

Gu H, Stein EA, Yang Y. Nonlinear responses of cerebral blood volume, blood flow and blood oxygenation signals during visual stimulation. Magnetic resonance imaging. 2005; 23(9):921–928.10.1016/j.mri.2005.09.007 [PubMed: 16310107]

Gutnisky DA, Dragoi V. Adaptive coding of visual information in neural populations. Nature. 2008; 452(7184):220–224.10.1038/nature06563 [PubMed: 18337822]

Hall CN, Klein-Flüge MC, Howarth C, Attwell D. Oxidative phosphorylation, not glycolysis, powers presynaptic and postsynaptic mechanisms underlying brain information processing. The Journal of neuroscience: the official journal of the Society for Neuroscience. 2012; 32(26):8940–8951.10.1523/JNEUROSCI.0026-12.2012 [PubMed: 22745494]

Heeger DJ, Huk AC, Geisler WS, Albrecht DG. Spikes versus BOLD: what does neuroimaging tell us about neuronal activity? Nature neuroscience. 2000; 3(7):631–633.10.1038/76572

Henson RN, Mouchlianitis E. Effect of spatial attention on stimulus-specific haemodynamic repetition effects. NeuroImage. 2007; 35(3):1317–1329.10.1016/j.neuroimage.2007.01.019 [PubMed: 17350862]

Herculano-Houzel S. Scaling of Brain Metabolism with a Fixed Energy Budget per Neuron: Implications for Neuronal Activity, Plasticity and Evolution. PLoS ONE. 2011; 6(3):e17514.10.1371/journal.pone.0017514 [PubMed: 21390261]

Howarth C, Gleeson P, Attwell D. Updated energy budgets for neural computation in the neocortex and cerebellum. Journal of cerebral blood flow and metabolism: official journal of the International Society of Cerebral Blood Flow and Metabolism. 2012; 32(7):1222–1232.10.1038/jcbfm.2012.35 [PubMed: 22434069]

Hyder F, Sanganahalli BG, Herman P, Coman D, Maandag NJG, Behar KL, Rothman DL. Neurovascular and Neurometabolic Couplings in Dynamic Calibrated fMRI: Transient Oxidative Neuroenergetics for Block-Design and Event-Related Paradigms. Frontiers in neuroenergetics. 2010; 210.3389/fnene.2010.00018

Kim T, Hendrich KS, Masamoto K, Kim SG. Arterial versus total blood volume changes during neural activity-induced cerebral blood flow change: implication for BOLD fMRI. Journal of Cerebral Blood Flow and Metabolism: Official Journal of the International Society of Cerebral Blood Flow and Metabolism. 2007; 27(6):1235–1247.10.1038/sj.jcbfm.9600429 [PubMed: 17180136]

Kim T, Kim SG. Temporal dynamics and spatial specificity of arterial and venous blood volume changes during visual stimulation: implication for BOLD quantification. Journal of cerebral blood flow and metabolism: official journal of the International Society of Cerebral Blood Flow and Metabolism. 2011; 31(5):1211–1222.10.1038/jcbfm.2010.226 [PubMed: 21179068]

Kohn A. Visual Adaptation: Physiology, Mechanisms, and Functional Benefits. Journal of Neurophysiology. 2007; 97(5):3155–3164.10.1152/jn.00086.2007 [PubMed: 17344377]

Larsson J, Smith AT. fMRI repetition suppression: neuronal adaptation or stimulus expectation? Cerebral cortex (New York, NY: 1991). 2012; 22(3):567–576.10.1093/cercor/bhr119

Laughlin SB. Energy as a constraint on the coding and processing of sensory information. Current opinion in neurobiology. 2001; 11(4):475–480. [PubMed: 11502395]

Leontiev O, Buxton RB. Reproducibility of BOLD, perfusion, and CMRO2 measurements with calibrated-BOLD fMRI. NeuroImage. 2007; 35(1):175–184.10.1016/j.neuroimage.2006.10.044 [PubMed: 17208013]

Levy WB, Baxter RA. Energy efficient neural codes. Neural computation. 1996; 8(3):531–543. [PubMed: 8868566]

Liang CL, Ances BM, Perthen JE, Moradi F, Liau J, Buracas GT, Buxton RB. Luminance contrast of a visual stimulus modulates the BOLD response more than the cerebral blood flow response in the human brain. NeuroImage. 2013; 64:104–111.10.1016/j.neuroimage.2012.08.077 [PubMed: 22963855]

Liu TT, Wong EC. A signal processing model for arterial spin labeling functional MRI. NeuroImage. 2005; 24(1):207–215.10.1016/j.neuroimage.2004.09.047 [PubMed: 15588612]

Liu Z, Rios C, Zhang N, Yang L, Chen W, He B. Linear and nonlinear relationships between visual stimuli, EEG and BOLD fMRI signals. NeuroImage. 2010; 50(3):1054–1066.10.1016/j.neuroimage.2010.01.017 [PubMed: 20079854]

Logothetis NK, Pauls J, Augath M, Trinath T, Oeltermann A. Neurophysiological investigation of the basis of the fMRI signal. Nature. 2001; 412(6843):150–157.10.1038/35084005 [PubMed: 11449264]

Mandeville JB, Marota JJ, Ayata C, Zaharchuk G, Moskowitz MA, Rosen BR, Weisskoff RM. Evidence of a cerebrovascular postarteriole windkessel with delayed compliance. Journal of cerebral blood flow and metabolism: official journal of the International Society of Cerebral Blood Flow and Metabolism. 1999; 19(6):679–689.10.1097/00004647-199906000-00012 [PubMed: 10366199]

Miller KL, Luh WM, Liu TT, Martinez A, Obata T, Wong EC, Buxton RB. Nonlinear temporal dynamics of the cerebral blood flow response. Human brain mapping. 2001; 13(1):1–12. [PubMed: 11284042]

Moradi F, Buračas GT, Buxton RB. Attention strongly increases oxygen metabolic response to stimulus in primary visual cortex. NeuroImage. 2012; 59(1):601–607.10.1016/j.neuroimage.2011.07.078 [PubMed: 21839179]

Murray SO, Olman CA, Kersten D. Spatially specific FMRI repetition effects in human visual cortex. Journal of neurophysiology. 2006; 95(4):2439–2445.10.1152/jn.01236.2005 [PubMed: 16394067]

Obata T, Liu TT, Miller KL, Luh WM, Wong EC, Frank LR, Buxton RB. Discrepancies between BOLD and flow dynamics in primary and supplementary motor areas: application of the balloon model to the interpretation of BOLD transients. NeuroImage. 2004; 21(1):144–153. [PubMed: 14741651]

Patterson CA, Wissig SC, Kohn A. Distinct Effects of Brief and Prolonged Adaptation on Orientation Tuning in Primary Visual Cortex. The Journal of Neuroscience. 2013; 33(2):532–543.10.1523/JNEUROSCI.3345-12.2013 [PubMed: 23303933]

Pfeuffer J, McCullough JC, Van de Moortele PF, Ugurbil K, Hu X. Spatial dependence of the nonlinear BOLD response at short stimulus duration. NeuroImage. 2003; 18(4):990–1000.10.1016/S1053-8119(03)00035-1 [PubMed: 12725773]

Poldrack RA. Region of interest analysis for fMRI. Social Cognitive and Affective Neuroscience. 2006; 2(1):67–70.10.1093/scan/nsm006 [PubMed: 18985121]

Restom K, Behzadi Y, Liu TT. Physiological noise reduction for arterial spin labeling functional MRI. NeuroImage. 2006; 31(3):1104–1115.10.1016/j.neuroimage.2006.01.026 [PubMed: 16533609]

Sanchez-Vives MV, Nowak LG, McCormick DA. Membrane mechanisms underlying contrast adaptation in cat area 17 in vivo. The Journal of neuroscience: the official journal of the Society for Neuroscience. 2000; 20(11):4267–4285. [PubMed: 10818163]

Sanganahalli BG, Herman P, Blumenfeld H, Hyder F. Oxidative Neuroenergetics in Event-Related Paradigms. The Journal of neuroscience: the official journal of the Society for Neuroscience. 2009; 29(6):1707–1718.10.1523/JNEUROSCI.5549-08.2009 [PubMed: 19211878]

Sclar G, Lennie P, DePriest DD. Contrast adaptation in striate cortex of macaque. Vision research. 1989; 29(7):747–755. [PubMed: 2623819]

Shin DD, Liu TT, Wong EC, Shankaranarayanan A, Jung Y. Pseudocontinuous arterial spin labeling with optimized tagging efficiency. Magnetic resonance in medicine: official journal of the Society of Magnetic Resonance in Medicine/Society of Magnetic Resonance in Medicine. 2012; 68(4): 1135–1144.10.1002/mrm.24113 [PubMed: 22234782]

Simon, AB.; Griffeth, VEM.; Wong, EC.; Buxton, RB. A Novel Method of Combining Blood Oxygenation and Blood Flow Sensitive Magnetic Resonance Imaging Techniques to Measure the Cerebral Blood Flow and Oxygen Metabolism Responses to an Unknown Neural Stimulus. In: Siegel, A., editor. PLoS ONE. Vol. 8. 2013. p. e54816

Solomon SG, Peirce JW, Dhruv NT, Lennie P. Profound contrast adaptation early in the visual pathway. Neuron. 2004; 42(1):155–162. [PubMed: 15066272]

Sutton BP, Noll DC, Fessler JA. Fast, iterative image reconstruction for MRI in the presence of field inhomogeneities. IEEE Transactions on Medical Imaging. 2003; 22(2):178–188. [PubMed: 12715994]

Uludağ K, Dubowitz DJ, Yoder EJ, Restom K, Liu TT, Buxton RB. Coupling of cerebral blood flow and oxygen consumption during physiological activation and deactivation measured with fMRI. NeuroImage. 2004; 23(1):148–155.10.1016/j.neuroimage.2004.05.013 [PubMed: 15325361]

Vazquez AL, Noll DC. Nonlinear aspects of the BOLD response in functional MRI. NeuroImage. 1998; 7(2):108–118.10.1006/nimg.1997.0316 [PubMed: 9558643]

Wager TD, Vazquez A, Hernandez L, Noll DC. Accounting for nonlinear BOLD effects in fMRI: parameter estimates and a model for prediction in rapid event-related studies. NeuroImage. 2005; 25(1):206–218.10.1016/j.neuroimage.2004.11.008 [PubMed: 15734356]

Wark B, Lundstrom BN, Fairhall A. Sensory adaptation. Current opinion in neurobiology. 2007; 17(4): 423–429.10.1016/j.conb.2007.07.001 [PubMed: 17714934]

Webster MA. Adaptation and visual coding. Journal of Vision. 2011; 11(5)10.1167/11.5.3

Weigelt S, Limbach K, Singer W, Kohler A. Orientation-selective functional magnetic resonance imaging adaptation in primary visual cortex revisited. Human brain mapping. 2012; 33(3):707–714.10.1002/hbm.21244 [PubMed: 21425395]

Weigelt S, Muckli L, Kohler A. Functional magnetic resonance adaptation in visual neuroscience. Reviews in the neurosciences. 2008; 19(4–5):363–380. [PubMed: 19145990]

Yeşilyurt B, Uğurbil K, Uludağ K. Dynamics and nonlinearities of the BOLD response at very short stimulus durations. Magnetic resonance imaging. 2008; 26(7):853–862.10.1016/j.mri.2008.01.008 [PubMed: 18479876]

Yi DJ, Kelley TA, Marois R, Chun MM. Attentional modulation of repetition attenuation is anatomically dissociable for scenes and faces. Brain research. 2006; 1080(1):53–62.10.1016/j.brainres.2006.01.090 [PubMed: 16507300]

Highlights

- Prolonged visual stimulation results in adaptation of cerebral metabolic rate of oxygen
- Adaptation also manifest as a sub-additive non-linearity of cerebral blood flow response
- CMRO2 adaptation is greater than flow, pointing to modulation of neurovascular coupling
- BOLD response depends strongly on the flow/metabolism ratio
- Differential adaptation of flow and metabolism cancels their effect on BOLD response

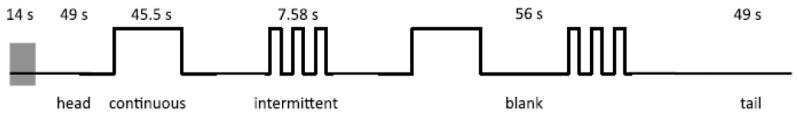

Figure 1.

Schematic diagram of timing of the peripheral stimulation. The order of presentation of intermittent and continuous epochs was counterbalanced across the runs. A central fixation task was presented throughout the whole run.

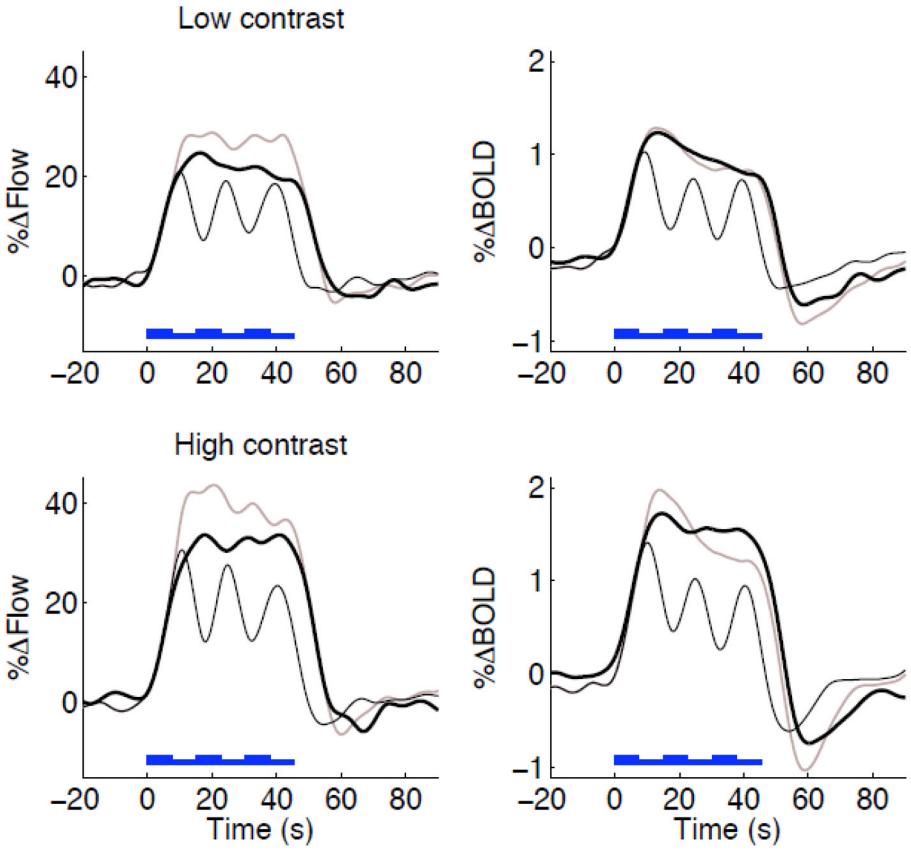

Figure 2.

Average flow and BOLD response time-courses for continuous (thick black curve) and intermittent (thin black curve) conditions. The observed response to intermittent stimulation was then used to predict the response for a linear system to the continuous stimulation (gray curve). A systematic difference between the predicted response and observed response to continuous stimulation would be an evidence of non-linearity, which may be due to adaptation. Top row, low contrast stimulus. Bottom row: high contrast stimulus.

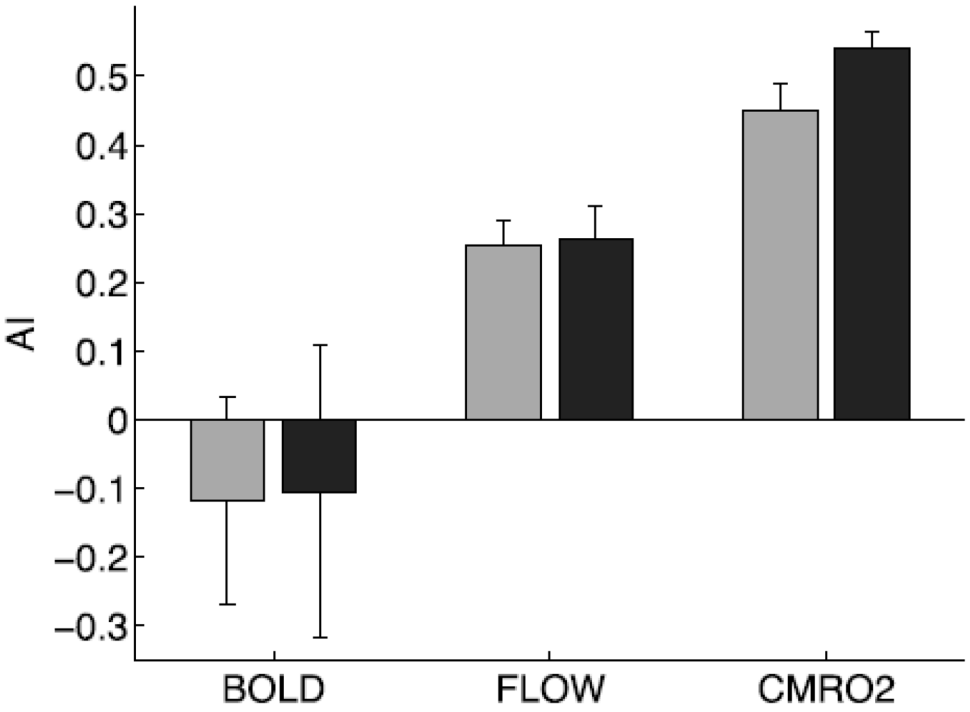

Figure 3.
Adaptation index (ordinate) for BOLD, flow, and oxygen metabolism for low- (gray) and high-(black) contrast stimuli. Error bars indicate SEM (across observers).

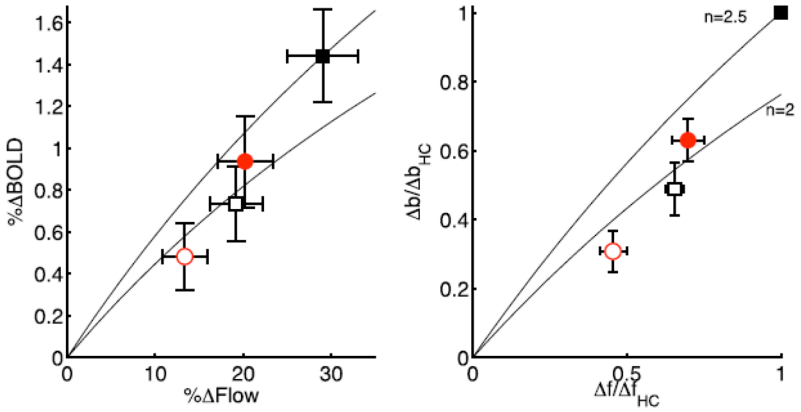

Figure 4.

The relationship between BOLD and flow responses to continuous (solid symbols) and intermittent (open symbols) stimulation. Black square: high contrast. Red circle: low contrast. The right plot depicts the same responses relative to the response to the high contrast continuous stimulation for each subject. The curves depict theoretical relationship between BOLD and flow changes for constant neurovascular coupling ratios of 2 and 2.5. Error bars indicate SEM (across observers).

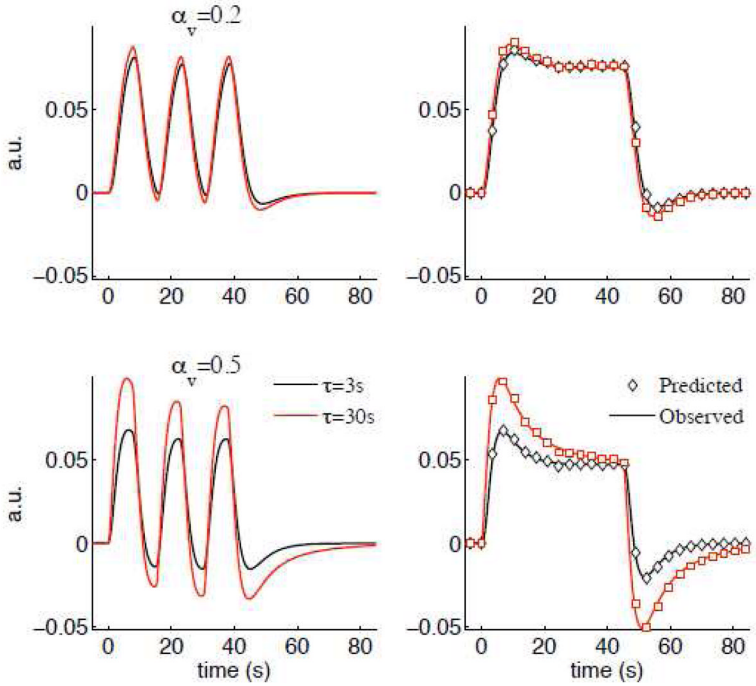

Figure 5.

Simulated BOLD responses to intermittent (left column) and continuous (right column) stimulation *without* adaptation of flow and metabolism. The response to continuous stimulus predicted from intermittent response is plotted for comparison (open symbols). Top row and bottom row depict different assumptions about the distribution of CBV change (arterial versus venous dominant change, respectively). Two curves in each subplot represent different assumptions about the time course of venous blood volume change (τ). a.u., arbitrary unit (corresponding to BOLD modulation due to increasing flow by 100%).