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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.

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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 and Engel, 2012; Patterson et al., 2013). Intrinsic synaptic and neuronal mechanisms and extrinsic network interactions may be important for adaptation (Dhruv et al., 2011; Ghisovan et al., 2008; Sanchez-Vives et al., 2000).

It has been suggested that adaptation optimizes neural coding efficiency (Adibi et al., 2013; Attneave, 1954; Cortes et al., 2012; Gutnisky and Dragoi, 2008; Wark et al., 2007; Webster, 2011). Neural computations are energy intensive (Attwell and Iadecola, 2002; Howarth et al., 2012) and the structural and functional organization of the cortex is subject to metabolic constraints (Herculano-Houzel, 2011; Laughlin, 2001; Levy and 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 et al., 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 and Finney, 2003; Murray et al., 2006; Weigelt et al., 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 ($n = \Delta CBF / \Delta CMRO_2$). Both bottom up and top-down inputs to early sensory areas can affect the coupling between metabolic and hemodynamic activities (Liang et al., 2013; Moradi et al., 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 (Buxton, 2010, 2012). Hemodynamic responses are nonlinear for very

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short stimulus durations (Gu et al., 2005; Uludağ et al., 2004; Yeşilyurt et al., 2008), possibly reflecting transient dynamics of cerebral blood flow and volume changes in cerebral cortex (Birn and Bandettini, 2005; 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 et al., 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 et al., 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 and 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 $CMRO_2$.

Methods

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.

Scan parameters

A multi-pulse pseudo-continuous arterial spin labeling sequence (Shin et al., 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 = 32 ms, 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 3 T whole body MRI scanner using the body coil for transmission and an 8-channel head coil receiver.

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 at 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 pseudo-random 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 (Fig. 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 TRs) 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 (Fig. 1), with the order of presentation counterbalanced across runs.

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

Analysis

The blurring of spiral images caused by field inhomogeneities was corrected based on an iterative algorithm (Sutton et al., 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 et al., 2000; Restom et al., 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 (Liu and 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.