Published in final edited form as:
Neuroimage. 2012 January 2; 59(1): 601–607. doi:10.1016/j.neuroimage.2011.07.078.

Attention strongly increases oxygen metabolic response to stimulus in primary visual cortex

Farshad Moradi[1], **Giedrius T. Buračas**[1], and **Richard B. Buxton**[1]

[1]Center for Functional MRI and Department of Radiology, University of California, San Diego, California

Abstract

Top-down attention enhances neural processing, but its effect on metabolic activity in primary visual cortex (V1) is unclear. Combined blood flow and oxygenation measurements provide the best tool for investigating modulations of oxidative metabolism. We measured the human V1 response to a peripheral low contrast stimulus using fMRI and found a larger fractional modulation of blood flow with attention compared to the blood oxygenation level dependent (BOLD) response, thus indicating a much larger modulation of oxygen metabolism than was previously thought. These findings point to different aspects of neural activity driving flow and metabolic changes to different degrees. We propose that V1 flow is driven strongly but not exclusively by the initial sensory-driven neural activity, which dominates the response in the unattended condition, while V1 oxygen metabolism is driven strongly by the overall neural activity, which is modulated by top-down signals related to attention.

1 Introduction

Voluntary attention improves detection and discrimination of visual stimuli by enhancing sensory processing in visual areas including V1. Neurons increase their firing rate in response to a stimulus when it is attended (Ito and Gilbert, 1999; McAdams and Reid, 2005; Motter, 1993), although this effect is rather small in V1 (Luck et al., 1997; Yoshor et al., 2007). In comparison, functional magnetic resonance imaging (fMRI) studies suggest a moderate attentional modulation of the blood oxygenation-level dependent (*BOLD*) signal in V1 (Brefczynski and DeYoe, 1999; Buracas and Boynton, 2007; Gandhi et al., 1999; Somers et al., 1999; Tootell et al., 1998). Interpretation of this phenomenon is problematic because of the intrinsic complexity of the *BOLD* signal and its primary dependence on changes in local deoxyhemoglobin: increased cerebral blood flow (*CBF*) drives the *BOLD* signal up, whereas, increased cerebral metabolic rate of oxygen ($CMRO_2$) drives the *BOLD* signal down. Both *CBF* and $CMRO_2$ are expected to increase with increased evoked neural activity, so the magnitude of the *BOLD* response depends strongly on the relative magnitudes of these underlying physiologic responses (Buxton, 2010).

The mechanisms underlying regulation of cerebral blood flow are not completely understood. A current hypothesis is that acute changes in *CBF* are primarily driven by fast

Correspondence information: Farshad Moradi, MD PhD, 200 W Arbor Dr, Dept. Radiology, UCSD Medical Center, MC 8756, San Diego, CA 92103-8756, fmoradi@ucsd.edu, Phone: (858) 822-0513, Fax: (858) 822-0605.

glutamate-mediated neural signaling, rather than biochemical feedbacks triggered by increased energy metabolism (Attwell and Iadecola, 2002). The cholinergic system may play an important role in regulation of local cerebral blood flow (Sato and Sato, 1995) and has also been implicated in attention (Herrero et al., 2008; Goard and Dan, 2009; Sarter et al., 2005). Stimulation of astrocytes is another important mechanism that appears to play a key role in neurovascular coupling (Iadecola and Nedergaard, 2007).

Depending on how top-down signals modulate the neurovascular coupling, the *BOLD* response may over- or underestimate metabolic activity. Top-down attentional mechanisms could drive a pure *CBF* increase in a preemptive fashion, with no increase in $CMRO_2$, producing a large *BOLD* response. Alternatively, top-down mechanisms could enhance the evoked activity and the $CMRO_2$ and *CBF* responses, and the modulation of the *BOLD* response would depend on the balance of these two effects. In contrast to the *BOLD* and *CBF* responses, $CMRO_2$ may simply increase as needed to meet the overall energy requirements of the evoked response.

We aimed to address two questions by using combined *CBF* and *BOLD* measurements to estimate relative $CMRO_2$ changes to the same visual stimulus when the subject was attending and not attending to the stimulus: does top-down attention increase V1 metabolic activity, and is top-down modulation of $CMRO_2$ less than or greater than *BOLD* modulation?

2 Materials and 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 24–35, three females, all subjects naive except FM) participated in the experiment.

2.2 Stimulus and Task

2.2.1 Main experiment—Subjects were instructed to fixate at the center of the screen and either perform a one-back memory task on digits appearing at fixation (control condition), or to monitor and report subtle contrast changes of a low-contrast peripheral grating (attention condition).

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. Low contrast (2% of the maximum display contrast) peripheral orthogonal sinusoidal (0.83 cpd) slowly drifting (0.25 Hz) gratings forming a dynamic plaid, were presented in the periphery. A symmetric trapezoid envelope was used: The contrast increased linearly from zero to maximum between 4.8° and 6.4° and decreased linearly to zero from 11.3° to 12.7° eccentricity (Figure 1).

Black digits (0.6°) appeared superimposed on fixation at 2 Hz (300 ms on, 200 ms off) in a pseudorandom order. In the control condition, at random intervals 3–7 seconds apart, the same digit would appear twice in a row, and the subject was allowed 1.5 s to press a key to indicate the repetition. The digits were also presented during the attention condition but the subjects were asked to ignore them.

At random intervals 3–7 s apart the contrast of the peripheral gratings was modulated +/− 45% of the average stimulus contrast (i.e., between 1.1% and 2.9% of maximum display contrast) with a sinusoidal profile (1 cycle, 100 ms). In the attention condition subjects were instructed to attend to the fixation while the peripheral grating is off, shift their attention to

the periphery before the grating was to be turned on (cued by an auditory beep before the grating onset), attend to the grating and report the changes in the contrast for 25 s, and shift attention to the center when the grating was turned off. In the control condition subjects were instructed to attend to the fixation for the duration of the run, continuously perform a one-back memory task on digits appearing at fixation, and completely ignore the peripheral gratings.

Baseline (fixation only) was acquired for 35 s at the beginning and at the end of each run.

Stimuli and task timing were identical in both attention and control runs (Figure 1).

2.2.2 Region of interest localizer and retinotopic mapping—Separate localizer runs using 100% contrast flickering peripheral gratings (square wave, 0.83 cpd, flickering at 7 Hz, subtending 5.6°–12° eccentricity at half maximum, Figure 1) were used to identify voxels corresponding to the position of the peripheral stimuli. A block design, using the same timing as the main experiment, was used.

Clockwise and counter-clockwise rotating wedges (120° width, 40 s cycle, 100% contrast checkerboard flickering at 8 Hz), were used in the separate retinotopy session. Subjects fixated at the center of the screen.

2.3 fMRI acquisition

The experiments were conducted in a 3 Tesla GE Signa Excite 3T whole body MRI scanner using the body coil transmission and an 8-channel head coil receiver. A quantitative arterial spin labeling (ASL) sequence with a dual-gradient echo spiral readout was used to simultaneously acquire *CBF* and *BOLD* responses. More specifically, we used a PICORE arterial spin labeling sequence in combination with QUIPPS II (Wong et al., 1998) (TR=2.5 s, TI_1 = 700 ms, TI_2 = 1500 ms, 20-cm oblique tag, 1-cm tag-slice gap) (Wong et al 1998) and a dual-echo gradient echo spiral readout (TE_1=9.4 ms, TE_2=30ms, flip angle 90°, FOV 24 cm, 64×64 matrix). This dual-echo approach allows the *BOLD* change to be measured quantitatively as a change in the transverse relaxation rate (R_2*), as well as the conventional percent signal change.

Seven oblique-coronal slices (7 mm thickness, no gap) covered the occipital cortex. Small diffusion gradients were applied before the first echo to suppress signal from larger arteries and draining veins (velocity > 2 cm/s). B_0 inhomogeneity maps were acquired using the same slice prescription. A high resolution structural image was acquired in each session, using a magnetization prepared 3D fast spoiled gradient acquisition in the steady state (FSPGR) sequence (124 axial slices, 1.3 mm slice thickness, TI 300 ms, TR 9.8 ms, TE 4 ms, 15° flip angle, FOV 25×18.75 cm_2, matrix 256×192). A second structural image was acquired for three subjects (when enough time was available at the end of the session) and the two images were averaged to improve signal to noise.

A separate session was dedicated to retinotopic mapping for each subject (except author FM). Multiple structural images (2–4) were acquired per subject and were averaged after coregistration to improve SNR. Imaging parameters for structural and functional scans were similar to the main experiment. For subject FM, retinotopic maps from a previous study were used (Moradi and Heeger, 2009).

2.3.1 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 (Restom et al., 2006; Glover et al., 2000). The data from the first 10 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).

Activation maps were generated from the physio-corrected localizer data using a general linear model (GLM). A region of interest (ROI) was defined from the flow maps for each subject (thresholded at $p<0.05$). Average time courses were obtained from this ROI. V1 borders were identified in a separate retinotopy session. ROI was limited to voxels inside V1. Structural images were coregistered and averaged, and cortical surface was reconstructed in FreeSurfer (Fischl et al., 1999; Dale et al., 1999). V1 borders were identified on the flattened cortical surface based on reversals of the polar angle maps (DeYoe et al., 1996; Engel et al., 1997, 1994; Sereno et al., 1995). Voxels for which V1 comprises half or more of the corresponding cortical surface are included.

We also analyzed the activity in ROIs defined based on *BOLD* activation maps ($p<0.05$) or a combination of BOLD and flow maps ($p_{\mathrm{Flow}}<0.05$ and $p_{\mathrm{BOLD}}<0.05$, $(p_{\mathrm{Flow}}+p_{\mathrm{BOLD}})/2<0.05$, see supplementary material). Average time courses obtained from active voxels outside V1 boundaries (extra-striate cortex) were analyzed separately (see supplementary figures S3 and S4 for comparison).

BOLD and *CBF* data were normalized by dividing the signal averaged over all voxels within the ROI to the average signal during head (35 s) and tail (35 s) baseline intervals. Although voxel-wise normalization could improve spatial uniformity of *BOLD* by correcting for intensity inhomogeneities, it was not possible for *CBF* because of much higher signal variability compared to BOLD. *CBF* is calculated from the first echo, which is less sensitive to B_0 inhomogeneity. R_2* changes, which are less sensitive than *BOLD* to intensity inhomogeneities, are presented in the supplementary material and parallel the *BOLD* findings. Compared to other studies that use voxel-wise normalization, our results are less dominated by voxels containing large draining veins and low baseline cerebral blood flow. By using an independent interval as the baseline (head and tail which are separate from stimulus and inter-stimulus epochs), we tried to avoid transient changes in $CMRO_2$ or cerebral venous blood volume during post-stimulus undershoot which could confound our measurements or introduce additional noise.

Amplitudes of the signals were averaged from 5s after the onset to 5 s after the offset of the gratings (stimulus-on), and 22.5 – 55 s after the offset of the gratings (stimulus-off). Response was defined as the difference between stimulus-on and stimulus-off signal normalized to the baseline value (that is, ΔCBF denotes $(CBF_{\mathrm{on}} - CBF_{\mathrm{off}})/CBF_{\mathrm{baseline}}$, similarly for $\Delta BOLD$ and $\Delta CMRO_2$).

Each run included a 25 s breath-hold interval followed by 35 s ad lib breathing at the end aimed to measure vascular reactivity in each subject (data not presented). These intervals were excluded from the analysis prior to correction for physiologic artifacts.

Normalized $CMRO_2$ response was estimated using a well-established model (Davis et al., 1998).

$$\Delta CMRO_2=\Delta CBF^{0.75}\,1-\frac{\Delta BOLD-1}{M}^{0.67}$$

M is a single parameter that captures multiple physiological variables underlying *BOLD* changes besides *CBF* and $CMRO_2$ and determines *BOLD* scaling. *M* was not measured in the current study and is assumed to be 0.12 (corresponding to a neurovascular coupling ratio of approximately 2.5 for the activity in high-contrast localizer runs consistent with our prior studies). Additional analysis using different models and a range of model parameters validated the results and demonstrated robustness of our findings (see Supplementary Material).

The coupling between blood flow and $CMRO_2$ (neurovascular coupling ratio) is defined as the ratio of normalized *CBF* response to the normalized $CMRO_2$ response.

Attention modulation index (*AI*) was calculated as follows:

$$AI_X = \frac{\Delta X_{Attention} - \Delta X_{Control}}{\Delta X_{Attention} + \Delta X_{Control}}$$

where *X* is either *CBF*, *BOLD*, or $CMRO_2$. *AI* of 0.5 indicates that the response with attention is three times the response in the control condition.

3 Results

We measured the V1 blood flow and oxygenation responses to peripheral low-contrast visual stimuli while subjects fixated at the center of the screen and either covertly attended to the periphery (attention runs) or ignored the periphery of the visual field (control runs). The *CBF* response (stimulus on minus off) in V1 region of interest to the peripheral stimulus significantly increased with attention (Figure 2 right panel, $F_{1,5}>21$, $p<.0001$). On average, flow increased 20.2±1.9% with attention (mean±SEM across 6 participants) and only 6.5±1% without attention (control). *BOLD* signal showed a similar but smaller attentional modulation (Figure 2 left panel, 0.91±0.1% vs. 0.6±0.05%, $F_{1,5}>23$, $p<.00001$, attention vs. control). This central finding, that the ratio of attended and unattended responses was approximately twice as large for *CBF* than for *BOLD*, is opposite what would be predicted for a pure *CBF* increase. More quantitatively, we analyzed these results in the context of models of the *BOLD* response to address the question: how much attentional modulation of $CMRO_2$ is required to explain this result?

Figure 3A shows the measured data with theoretical predictions based on a standard model (Davis et al., 1998) that describes the relationship between *BOLD*, *CBF*, and $CMRO_2$. In this model, the *BOLD* response depends nonlinearly on the *CBF* response, and is modulated by two additional parameters: a scaling parameter that is related to the amount of deoxyhemoglobin present in the baseline state, and the coupling ratio of the fractional change in *CBF* to the fractional change in $CMRO_2$. In figure 3A, the model prediction is based on typical values of the scaling parameter we have measured in other studies. The increase of *BOLD* response with attention was smaller than predicted for a pure flow increase, or even a proportional increase in $CMRO_2$ and blood flow changes.

The current data is consistent with a $CMRO_2$ change of 1.1±0.8% without attention, and 8.6±1.1% with attention, corresponding to a large decrease of the flow-metabolism coupling ratio ($\Delta CBF/\Delta CMRO_2$). The difference of the $CMRO_2$ responses with and without attention was approximately 7.5% of the baseline $CMRO_2$ value ($F_{1,5}>12.9$, $p=.0005$). These values correspond to the neurovascular coupling ratio of 4.5 for unattended, and 2.25 for attended stimulus response.

To compare the magnitude of attentional modulation of different signals, an attention modulation index (*AI*, Figure 3B) was calculated by dividing the difference of the responses to visual stimulus in the attention and control conditions by their sum. A two-way ANOVA showed a significant effect of signal type (flow, *BOLD*, or metabolism) in V1 ($F_{2,5}$=6.3, p=.017). The attentional modulation of estimated metabolism was more than twice that of *BOLD*. Post-hoc testing showed a significant difference between attention modulation for *BOLD* and $CMRO_2$.

Unlike *BOLD* and flow which were directly measured, $CMRO_2$ changes are calculated based on certain assumptions. Estimated $CMRO_2$ responses to each condition depends on the value of the scaling parameter *M*, which was not measured in this study. Are there conditions under which the observed increase in *BOLD* and flow measurements with visual attention could occur without any increase in oxygen 8 metabolism? Or perhaps, could the fractional increase in metabolic activity be more modest, similar to what is observed with *BOLD*? Our results appear to be at odds with those possibilities. The estimated $CMRO_2$ response in attention and control conditions varies as a function of the *BOLD* scaling parameter *M* (Figure 4A). The difference in the two $CMRO_2$ responses, however, remains positive over the whole range. Moreover, the fractional modulation of $CMRO_2$ is markedly larger than *BOLD* modulation, regardless of M (Figure 4B).

Similar results were obtained using different $CMRO_2$ models and for a wide range of model parameters. Methodological considerations are discussed in details in the supplementary material.

4 Discussion

To our knowledge this study is the first to demonstrate that arterial spin labeling (ASL) can be used to study modulation of *CBF* by top-down neural processes related to attention. ASL has lower signal to noise ratio and provides lower spatial and temporal resolution than *BOLD*. Quantitative ASL techniques such as QUIPSS-II provide an even lower SNR (which is necessary to eliminate or reduce the effect of transit time changes). Nonetheless, these techniques provide complementary information that is essential for interpretation of the *BOLD* changes. Specifically for this study, the combination of *CBF* and *BOLD* measurements makes possible estimates of the modulation of $CMRO_2$ with attention. Unlike *BOLD*, $CMRO_2$ is a physiological parameter directly related to total neural activity, and not vascular factors.

We found that directing attention to a visual stimulus in a peripheral location modulated the *CBF* response to the stimulus more than the *BOLD* response, in the sense that the ratio of the response magnitudes was about twice as large for *CBF* compared with *BOLD*. Analyzed in the context of models of the *BOLD* response, these data imply an even stronger modulation of the $CMRO_2$ response. An attentional modulation of flow with no increase or even a fractional increase in metabolic activity proportional to the increase in *BOLD* response, are inconsistent with our data.

The visual input was identical in attention and control conditions. Therefore, the modulation of metabolic activity could be attributed to top-down signals related to manipulation of attention, arousal, task, and memory. It is difficult to know exactly the contribution of each feature to the spatially selective increase in V1. However, task difficulty and structure were similar in both conditions. Therefore, manipulation of spatial attention is likely to be the main contributor to our results.

Modulation of *CBF* and *BOLD* activity in the absence of significant spiking and LFP changes (e.g., (Sirotin and Das, 2009) but see (Handwerker and Bandettini, 2010)) could

potentially arise if the *CBF* response is strongly modulated by a small component of the overall neural response that does not strongly modulate measured spiking and LFP signals. If the overall neuronal activity response is weak, so that there is little change in $CMRO_2$, but the *CBF* response is strong, then a prominent *BOLD* response would result. This scenario suggests the possibility that attention could strongly modulate *CBF* with little effect on $CMRO_2$, creating a strong modulation of the *BOLD* response when a stimulus is attended compared to when it is not attended. However, our current results do not support this picture.

Our observation of a strong modulation of the $CMRO_2$ response with attention is surprising given that the modulation of V1 firing activity is found to be much weaker. In a recent study (Chen et al., 2008) the attention modulation index (*AI*) for firing activity was reported to be 0.03 – 0.09, compared with our current observation of 0.8 for $CMRO_2$. The source of this large mismatch between modulation of spiking activity and oxygen metabolism is unknown, and worth further study. One possibility is that attention modulates the number of neurons involved in the overall evoked response more than it modulates the specific response of a single neuron activated by the stimulus. Because of the coarse spatial scale of imaging measurements, such a recruitment of neuronal involvement would strongly increase the net $CMRO_2$ increase within an imaging voxel. This could be compatible with a more modest modulation of the activity of the neurons that respond most consistently to the stimulus and would be chosen to be analyzed in an electrode study. A second possibility is related to the idea that in the awake brain there is always a balance of excitatory and inhibitory activity. If attention increases the evoked response of both excitatory and inhibitory activity, the $CMRO_2$ would be expected to increase because of the energy costs of transporting ions. However, the firing of particular neurons depends on the balance of excitatory and inhibitory activity. Thus, in a crude sense $CMRO_2$ would depend on the sum of excitatory and inhibitory activity, while spiking would depend on the difference. These possibilities highlight the idea that metabolism measurements can potentially provide information that is complementary to that provided by electrophysiology.

We also found a strong modulation of flow and metabolic activity in visual voxels outside of V1 (Supplementary Figures S5 and S6). Given the large size of voxels in the present study, a small part of the signal we attribute to V1 arises in extrastriate visual cortex. However, given the very similar degree of attentional modulation inside and outside the presumed V1, the effect of partial voluming appears to be negligible.

The act of attending to the stimulus could potentially alter the level of brain activity during the off periods between stimuli. *BOLD* and *CBF* during inter-stimulus intervals (off periods) were both slightly lower than the baseline (although this was not statistically significant). Also, the *BOLD* post-stimulus undershoot was slightly larger in attention runs than in control runs. However, this difference did not reach significance. In principle, because the relationship between *BOLD*, *CBF*, and $CMRO_2$ is non-linear, a large difference between inter-stimulus signals in the attention and control conditions could have complicated the interpretation of our results. However, the level of change we observed suggests that this should not be a large effect in the current study.

Eye movements were not recorded in the present study. Eye movements can evoke or suppress a *BOLD* response in V1 (Sylvester et al., 2005; Sylvester and Rees, 2006; Vallines and Greenlee, 2006), and therefore contamination of *BOLD* modulations with eye movement related signal has been a concern in studies of attention. Human subjects, however, have been shown to maintain good fixation while attending to the peripheral surround, and their eye movements are not different from when they attend to the center (Moradi et al., 2007; Somers et al., 1999). In our study, the contribution of eye movements to the attentional

enhancement is likely to be negligible. It is worth noting that *BOLD* signal changes that correlate with eye-movements are likely due to top-down mechanisms (Chahine and Krekelberg, 2009) rather than being caused by motion of the retinal image (bottom-up). Retinal input change due to eye movement does not explain a decrease in *CBF*/$CMRO_2$ coupling or the discrepancy between AI_{BOLD} and AI_{CMRO2}.

BOLD fMRI is a crude tool for studying brain activation. *BOLD* signal correlates with spiking (Mukamel et al., 2005) and synaptic activity (Viswanathan and Freeman, 2007), but *BOLD* signal is sensitive to vascular and metabolic factors as well. Current models of neurovascular coupling are incomplete (Handwerker and Bandettini, 2010), and coupling varies across the brain (Ekstrom et al., 2009). In addition to variability in the way *CBF* responds to neural activity, the *BOLD* effect depends on the balance of changes in *CBF* and $CMRO_2$, because that is what affects the oxygenation of the blood. The ratio of the changes in *CBF* and $CMRO_2$ varies across the brain (Ances et al., 2008; Chiarelli et al., 2007), and even within one brain region varies with stimulus amplitude (Lin et al., 2008). In short, the complexity of the *BOLD* response precludes a simple interpretation of the magnitude of the *BOLD* response as a quantitative reflection of the magnitude of the underlying change in neural activity. However, the current study demonstrates that a quantitative fMRI approach combining *CBF* and *BOLD* measurements allows us to separate the changes in *CBF* and $CMRO_2$ and begin to relate these physiologic changes to specific aspects of neural activity.

Several studies, using fMRI and positron emission tomography (PET) methods, found that the ratio of the fractional changes in *CBF* and $CMRO_2$ increased in visual cortex when the flicker frequency of the stimulus increased (Lin et al., 2008; Vafaee and Gjedde, 2000), and our group recently found a similar effect when the contrast of the checkerboard was increased (Liang et al. Proc. ISMRM, 2009, abstract 1630). In studies of neural activity the increased response with attention is often described as equivalent to increasing the strength of the stimulus (Reynolds et al., 2000). If that correspondence held for *CBF*/$CMRO_2$ coupling, we would expect the current experiment to have shown an increased *CBF*/$CMRO_2$ coupling ratio for the attended stimulus. Instead we found the opposite. A possible explanation for this finding is that *CBF* and $CMRO_2$ are driven to different degrees by different aspects of the evoked neural activity. A potentially useful distinction is to consider the initial sensory-driven component separately from the overall cortical response. Assuming that the sensory-driven component exerts a larger effect on *CBF* than the overall response, the *CBF*/$CMRO_2$ coupling ratio increases whenever the sensory-driven component increases disproportionately more than the overall neural response. This could occur when the input to the brain area increases (i.e., by increasing flicker frequency or contrast), but the overall response is near saturation. In a complementary way, if the result of attention is to increase the overall evoked neural response to the same input, then attention should reduce *CBF*/$CMRO_2$ coupling ratio, as we found in the current study. This greater response of *CBF* to the initial sensory-driven activity could be viewed as a feed-forward mechanism that anticipates a need for increased delivery of oxygen before the demand for oxygen has fully developed. Further studies are needed to test this hypothesis.

5 Conclusion

The unexpected finding of this study is that blood flow is more strongly modulated by attention than the *BOLD* response. Based on our understanding of the *BOLD* effect, this phenomenon implies that the oxygen metabolism response, which is the energetic footprint of cortical computations, is even more strongly modulated than the *BOLD* or flow responses. Specifically, an unattended stimulus evokes a flow response with relatively little oxygen metabolism response, but with attention the same stimulus evokes a larger flow response and a much larger oxygen metabolism response. This pattern is consistent with different

aspects of neural activity driving the flow and metabolism changes to different degrees, with the initial sensory-driven activity disproportionately affecting the modulation of *CBF*. These results demonstrate that combined measurements of flow and metabolism changes can provide a window on different aspects of neural activity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Supported by NIH T32-EB005970, NS-36722, and UCSD Center for Functional MRI.

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Highlights

- Attention strongly modulates cerebral blood flow and oxygen metabolism in V1.
- CMRO2 modulation is larger than expected from electrophysiology and BOLD fMRI studies.
- Attention reduced $CBF/CMRO_2$ coupling ratio.
- Different aspects of neural activity drive flow and metabolism to different degrees.

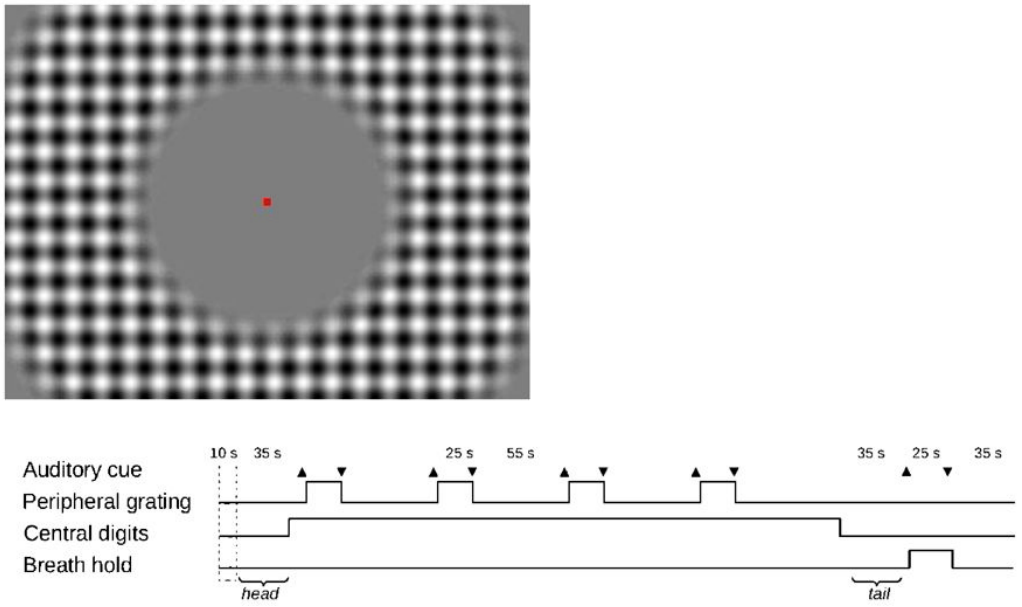

Figure 1.
Stimulus. Top: Peripheral grating (100% contrast. For the main experiment the same grating at 2% contrast was used). The display subtends 22°×16°. Bottom: Timing of the epochs in each run (same for attention and control runs).

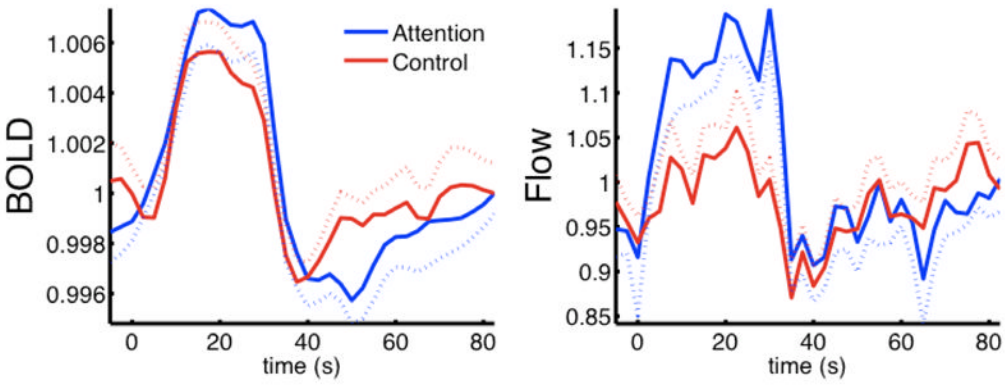

Figure 2.
Visual activation time courses in response to the peripheral grating when it was attended (blue) vs. when the subjects were engaged in a fixation task (red), averaged across all subjects. Dotted lines indicate SEM.

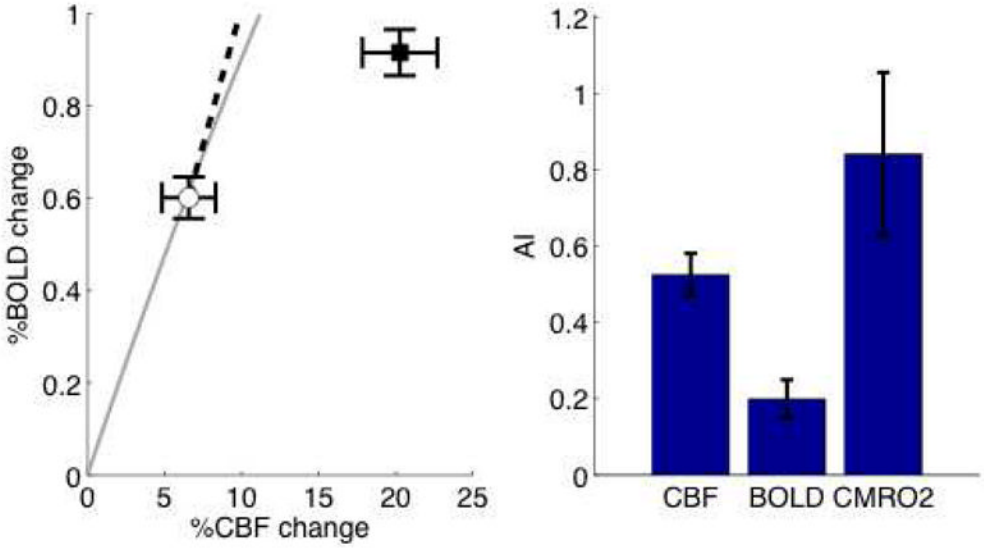

Figure 3.

Attentional modulation of $CMRO_2$ and neurovascular coupling. **A**) Magnitude of the evoked BOLD and CBF responses for unattended (open circle) vs. attended stimulus (solid square). Also shown are theoretical BOLD/CBF curves for a proportional increase in flow and metabolism with attention (solid) vs. increase in flow without an increase of metabolism (dashed). Any point on the right side of the solid curve indicates a disproportional increase in $CMRO_2$ vs. flow (i.e., decreased coupling ratio). Error bars: SEM across trials. See also Figure S1. **B**) Attention modulates flow and metabolism more than BOLD. AI: attention modulation index. Error bars: SEM (across subjects).

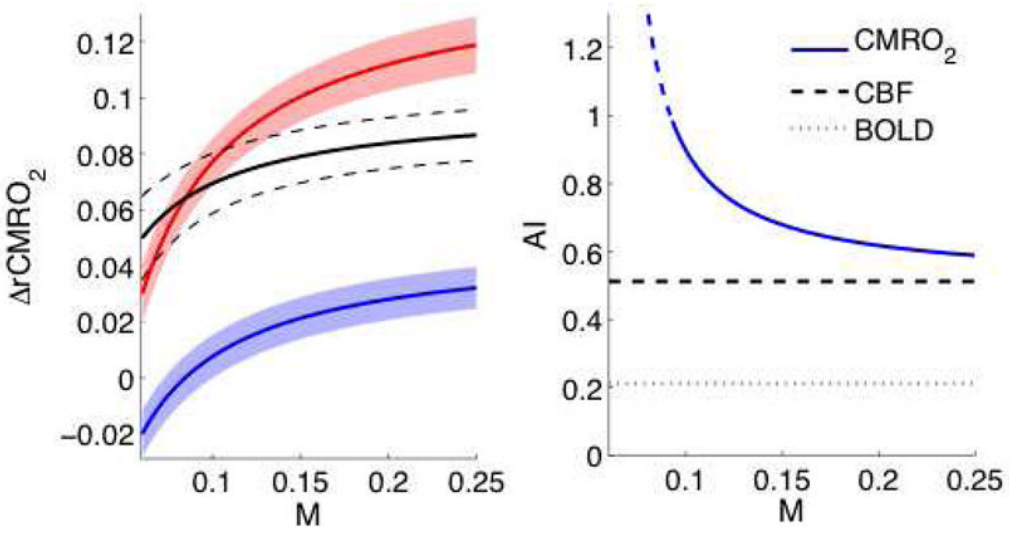

Figure 4.

A) Estimated $CMRO_2$ response for unattended (blue curve) vs. attended stimulus (red) as a function of BOLD scaling parameter. The difference (black curve) indicates increased metabolism attributable to top-down signals. Shaded area indicates SEM across subjects. **B**) Estimated attentional modulation of metabolic activity (AI_{CMRO2}) as a function of BOLD scaling parameter M. For low values of M, our data is compatible with a negative metabolic response to stimulus without attention and consequently the AI is greater than one (dashed segment). AI_{Flow} and AI_{BOLD} are depicted for comparison.