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Negative BOLD in the Visual Cortex: Evidence Against Blood Stealing

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Abstract: The positive BOLD (blood oxygen level-dependent) response elicited in human visual cortex by a localized visual stimulus is accompanied by a reduction in the BOLD response in regions of the visual cortex that represent unstimulated locations in the visual field. We have suggested previously that this negative BOLD reflects attention-related suppression of neural activity, but it might also be explained in terms of "blood stealing," i.e., hemodynamic changes that have no neural correlate. We distinguish two possible hemodynamic effects of this type: (1) blood flow reduction caused by locally reduced pressure in vessels that share their blood supply with nearby dilated vessels; and (2) blood flow reduction caused by active constriction of vessels under neural control. The first is ruled out as an explanation of negative BOLD by showing that a visual stimulus that stimulates primary visual cortex in one hemisphere can cause extensive suppression in the other hemisphere i.e., it is not a local phenomenon. Negative BOLD most likely reflects suppression of neural activity, but could also reflect an active blood flow control system. *Hum. Brain Mapp. 21:213–220, 2004.* © 2004 Wiley-Liss, Inc.

Key words: fMRI; BOLD; vision; attention; striate cortex; extrastriate cortex

INTRODUCTION

The BOLD (blood oxygen level-dependent) effect [Ogawa et al., 1990] has been used widely in functional magnetic resonance imaging (fMRI) as an index of activity levels in the human cerebral cortex. In particular, a localized positive BOLD contrast between a task and a no-task interval or event is interpreted commonly as evidence for task-related processing in the cortical region concerned.

A few studies have also noted negative BOLD responses that are associated with some task, stimulus or event. An example of negative BOLD was reported by Smith et al. [2000]. They showed that when an observer views a small, flickering target pattern in an otherwise uniform grey visual field, the resulting region of activation (positive BOLD) in the primary visual cortex is surrounded by an extensive area of negative BOLD. This affects much of the visual cortex, apart from the activated area. The negative BOLD phenomenon was interpreted in terms of attentional modulation. When a pattern appears in a blank field, it attracts the observer's attention. The observer's limited attentional resources, which were previously spatially diffuse, become focused at one location. As a result, all other locations suffer a reduction in attention. If spatial attention causes changes in baseline neural activity levels, as has been suggested [Luck et al., 1997], then withdrawal of attention from an unstimulated region of the visual field is expected to result in reduced neural activity and hence a reduction in the BOLD response. Smith et al. [2000] conducted experimental manipulations of attention and demonstrated variations in the magnitude of the negative BOLD response that were consistent with this interpretation.

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The term "negative BOLD" has also been used in two other contexts: (1) undershoot of the baseline on cessation of stimulation [Jones et al., 1998]; and (2) the small initial dip seen in the BOLD response at short latencies [Ernst and Hennig, 1994]. We use it here exclusively to refer to voxels that show sustained negative responses to a visual stimulus that causes positive activation elsewhere. The phenomenon of negative BOLD in the occipital cortex has been noted by various other authors [e.g., Saad et al., 2001; Tootell et al., 1998a,b] and is also seen with positron emission tomography (PET) [Shulman et al., 1997]. As well as studies of negative BOLD in the visual cortex, there are both PET and fMRI studies of deactivation of one sensory modality or cognitive system in association with activation of another [e.g., Ghatan et al., 1998; Hutchinson et al., 1999; Shulman et al., 1997]. It is unclear whether this reflects similar processes to negative BOLD in unstimulated portions of visual cortex.

Although the occurrence of negative BOLD in occipital cortex is not in doubt, its interpretation is controversial. Shmuel et al. [2002], noting a strong amplitude correlation and a similar time course between the positive, stimulus-related BOLD response in the stimulated region and the negative effect in nearby voxels, raised the possibility that the negative effect might reflect "blood stealing," i.e., the elevation of blood flow at the activated location causes reductions in blood supply in nearby areas sharing the same blood vasculature. If this were correct, negative BOLD could occur with no concomitant reduction in neural activity and could be a purely hemodynamic effect with no immediate significance for neural processing. Shmuel et al. [2002] estimated oxygen consumption ($CMRO_2$) by comparing BOLD to flow measurements obtained from perfusion imaging and calculated that negative BOLD is associated with reduced $CMRO_2$. This suggests that negative BOLD is associated with reduced neural activity, but direct evidence is lacking.

We show that negative BOLD in the human occipital cortex cannot be explained purely in terms of local blood stealing.

MATERIALS AND METHODS

The purpose of the experiment was to provide a strong test of the possibility that the negative BOLD response seen in unstimulated parts of the visual cortex simply reflects reduced blood flow occurring as a result of reduced local blood pressure, without any concomitant neural activity. The rationale of the experiment is based on the premise that any such blood stealing can only be local. It is easy to imagine that blood stealing might occur from nearby capillaries supplied by the same artery, but unlikely that blood is stolen in measurable quantities from vessels fed by a different artery. Specifically, because the two cerebral hemispheres have essentially independent blood supplies via the two carotid arteries, we would not expect localized activity in one hemisphere to result in reduced blood flow in the other. Strong evidence against blood stealing would therefore be obtained if it could be shown that negative BOLD can occur in the cerebral hemisphere contralateral to the one showing the positive, stimulus-related BOLD activity.

At the level of the primary visual cortex, it is simple to arrange for a visual stimulus to activate one hemisphere only and then to test for BOLD changes in the other. Because each hemisphere represents one visual hemifield, all that is necessary is to position the stimulus to one side of a fixation point. If negative BOLD reflects neural suppression, perhaps related to a reduction in the allocation of attention to unstimulated areas of the visual field [Smith et al., 2000], we might expect it to appear in the cortex representing all parts of the visual field around the stimulated area. This includes field locations on the opposite side of the vertical meridian from the stimulus, which are represented in the other hemisphere. A peripheral visual stimulus should thus cause activation only in the contralateral visual cortex (with respect to the stimulus), and should cause suppression in both the surrounding contralateral cortex and in the ipsilateral visual cortex. Some observations made by Tootell et al. [1998b] in a study using unilateral visual stimulation suggest that this may be the case. On the other hand, if negative BOLD reflects blood stealing, suppression may spread as far as the representation of the vertical meridian in the contralateral hemisphere, but not to ipsilateral cortex.

Participants

The participants were five healthy adults (the three authors and two volunteers) who were paid for their time. They were screened in accordance with standard procedures and informed consent was obtained in writing.

Visual Stimulation

Visual stimuli were generated by a computer and were displayed on a rear-projection screen by means of a LCD projector (resolution = 1,024 × 768). The participant lay supine in the scanner, and looked with the dominant eye into a custom-built optical device that magnified the image on the screen. This gave a monocular, circular image of diameter 27 degrees. The nondominant eye was occluded. The mean luminance of the image was approximately 240 cd/m^2.

The visual stimulus was a high-contrast, horizontally oriented sine grating presented to one side (left or right) of a central fixation spot (Fig. 1). The grating moved continuously (either up or down) within a stationary circular aperture, with a drift temporal frequency of 5 Hz. The direction of drift of the grating was randomly reassigned, giving it a 50% probability of changing direction, every 860 msec. The stimulus was presented in a block design (15 sec on, 15 sec off) with eight cycles (total 4 min). During off phases, the grating was replaced by a blank field of the same mean luminance. The fixation spot was continuously present. To ensure that attention was fully engaged on the grating stimulus, when present, the subject was instructed to count the total number of direction reversals seen during the course of the 4-min experiment, while maintaining fixation at all times. The count, given verbally after the end of the exper-

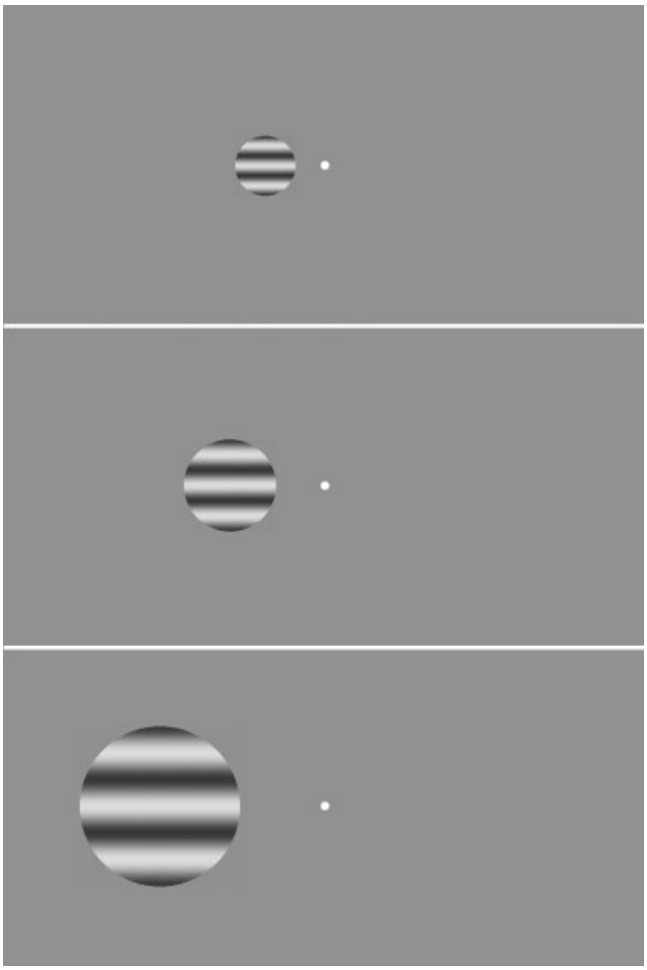

Figure 1.
Visual stimuli used in the experiment. In all cases, the participant fixated the central spot and a grating was presented to one side (either left, as shown, or right). The gratings drifted vertically at 5 Hz and changed direction (up/down) unpredictably. Three different grating patches of different sizes, eccentricities, and spatial frequencies were used.

iment, was compared to the actual number of reversals. The data were rejected if the count was not within 10% of the correct figure.

Three different stimulus eccentricities were employed (1, 2, and 4°, respectively). With a low eccentricity, there is a risk that even quite small eye movements could cause direct activation of the ipsilateral cortex, which in turn could cause ipsilateral suppression. Any significant ipsilateral activation would be readily detectable, but the validity of the experiment would be destroyed. A high eccentricity therefore provides a stronger test, but might generate neural suppression that fails to reach ipsilateral cortex simply because it is too far away. We therefore repeated the experiment at each of three eccentricities (Fig. 1). To produce both equivalent visibility and equivalent cortical activation areas for the three stimuli, the grating stimulus was scaled in size according to the cortical magnification factor, M [Rovamo et al., 1978]. The diameter of the grating (in terms of visual angle) was 1.5, 2.3, or 4.0 degrees at eccentricities of 1, 2, and 4 degrees, respectively. The stimulus spatial frequency (bar width) was also scaled and was 2.0, 1.3, and 0.74 c/degrees, respectively. The drift speed increased with eccentricity to maintain the constant drift temporal frequency of 5 Hz. Left and right hemifields were stimulated, in separate conditions, making a total of six stimulus conditions.

Data Acquisition

Imaging was carried out with a 1.5-T whole-body GE LX/Nvi scanner equipped with a 40 mT/m gradient system. The participant was positioned with the head in an RF receive-transmit headcoil. Local variations in blood oxygenation (BOLD response) were measured using susceptibility-based fMRI, applying gradient-recalled echo-planar imaging (EPI) sequences.

Twenty-four parallel, 3-mm thick planes were imaged using a T2*-weighted sequence (TR = 3,000 msec; TE = 40 msec; field of view = 190 mm; 64 × 64 voxels). The planes were axial and were positioned with the aid of a midsagittal T1-weighted scout image to include the entire occipital lobe in both hemispheres. Each experimental run lasted for 4 min, during which time functional images were acquired continuously.

For each participant, sagittal T1-weighted images of the posterior third of the brain were acquired (voxel size = 0.78 × 0.78 × 1.6 mm). These were used to determine the anatomic localization of functional responses.

Data Analysis

Activation profiles were analyzed and visualized using a combination of *SPM2* (Wellcome Department of Imaging Neuroscience, London, UK), *BrainTools* (Aston University, Birmingham, UK), and *Vista Software* (Stanford, CA), employing a general linear model approach. To compensate for any movement of the head, functional volumes were realigned and resliced. Spatial smoothing of the functional signal was also carried out by convolution with a 3D Gaussian kernel (full-width half-maximum [FWHM], 4 mm). Low-frequency effects were removed using a high-pass filter (cutoff, 128 sec). Image intensity normalization was not employed, because this could potentially introduce artificial negative BOLD changes. A square wave function convolved with a standard hemodynamic response function was used to estimate contrasts of interest. Voxel-by-voxel hypotheses were tested with a t statistic to provide statistical parametric maps where positive t values represented stimulus-related activation and negative values reflected negative BOLD.

For three of five subjects, retinotopic maps of the early visual areas were obtained in separate experiments and data from the main experiment were co-registered with these maps. Retinotopic mapping was carried out using conventional procedures and analysis [Engel et al., 1997; Sereno et al., 1995]. The temporal phase of the response to a slowly

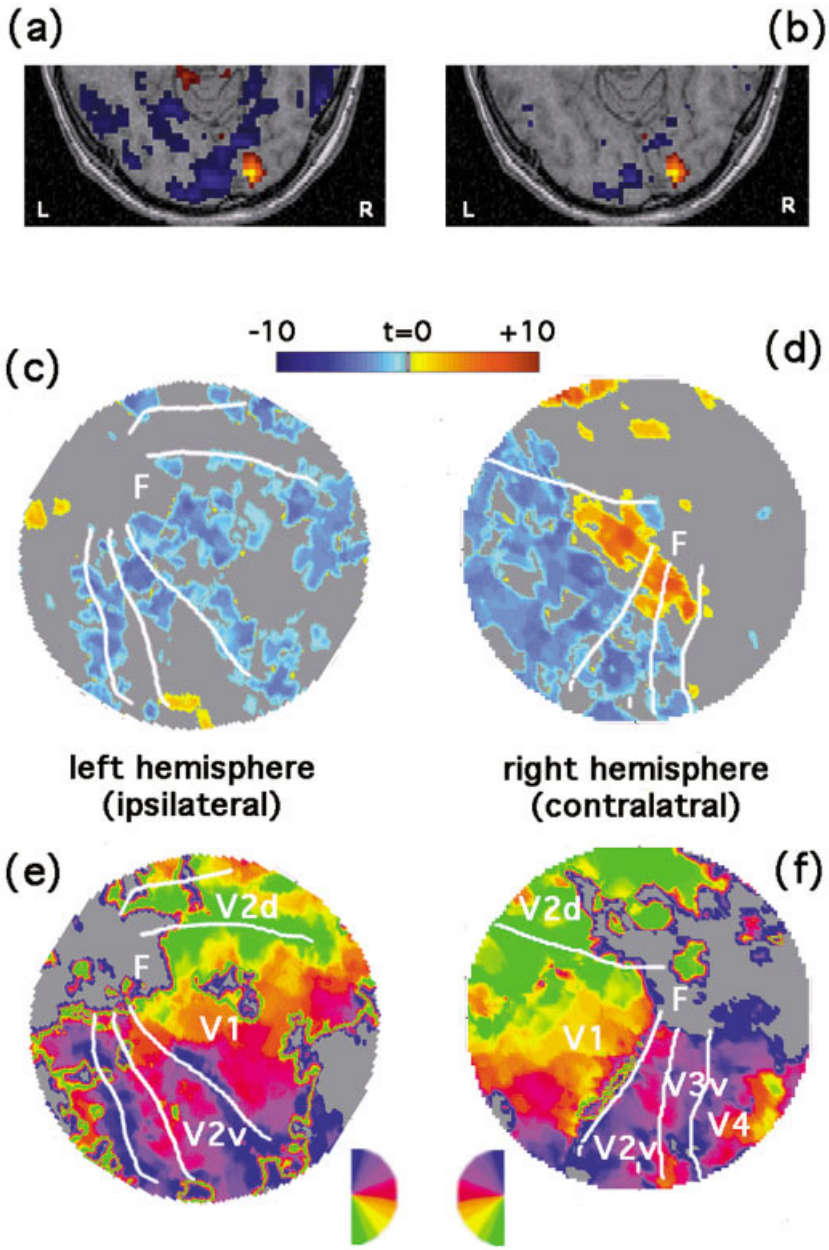

Figure 2.
Results from one subject (A.W.) in one condition (stimulus on the left, eccentricity 1°) shown as colored overlays. **a,b:** Results overlaid on a horizontal slice through occipital cortex, shown in neurologic convention (left hemisphere on the left). Colors represent the magnitude of the BOLD response in each voxel. Positive BOLD is shown as red/yellow, negative BOLD as blue. The left image is thresholded at $P < 0.5$ and the right image shows the same data thresholded at $P < 0.01$. **c,d:** Results shown on a flattened representation of the grey matter of the occipital cortex. Each flatmap is centered in the calcarine sulcus and has a radius of 45 mm. Colors represent *t* scores (see key). Positive *t*, positive BOLD; negative *t*, negative BOLD. Data are thresholded at $P < 0.01$. **e,f:** The same flatmaps showing the results of a phase-mapping experiment. The colors represent visual field positions (see key) and the white lines mark approximate locations of the boundaries between visual areas. These boundaries are also marked on the flatmaps in (c) and (d).

rotating, flickering checkerboard wedge was established for each voxel in the posterior occipital cortex. The phases were superimposed as colors on a flattened representation of the grey matter surface produced using *Stanford Tools*. These phases were used to estimate the positions of the boundaries between visual areas.

RESULTS

Individual Analyses

All five subjects showed negative BOLD in non-stimulated regions of the visual cortex. This suppression was always evident in the ipsilateral and the contralateral hemisphere. Typical results are illustrated in Figure 2 for one participant (A.W.) in one condition (stimulus presented in the left hemifield at an eccentricity of 1°, as in top panel of Fig. 1). Figure 2a and 2b show results as color overlays on a typical horizontal slice through occipital cortex. Color represents the amplitude of the main component of interest. In the right hemisphere only, positive BOLD (red/yellow) is seen close to the occipital pole (foveal representation). This reflects the response to the flickering grating stimulus in the contralateral visual field. Elsewhere in the slice, voxels are either inactive or show negative BOLD (blue). Voxels showing negative BOLD are plentiful when only a very low threshold is applied (Fig. 2a) but become quite sparse when

even a moderate ($P < 0.01$) threshold is used (Fig. 2b). They are present in both the contralateral and ipsilateral hemispheres.

Figure 2c and 2d show data from the same participant and stimulus condition as color overlays on a flattened representation of the occipital cortex of each hemisphere. Colors represent t values (see key) and are thresholded at $P < 0.01$ (uncorrected). Also shown are the boundaries of the visual areas, derived from retinotopic mapping results in the same subject (Fig. 2e,f). Again, in the right (contralateral) hemisphere (Fig. 2d), positive BOLD (red/yellow) is seen close to the foveal representation. It is present within both V1 and the adjoining visual areas, as expected. Adjacent to this is a large area containing many voxels that show negative BOLD (blue). This area corresponds to the representation of unstimulated portions of the visual field in V1 and also extends into V2 and V3, at least on the ventral side. Notably, the negative BOLD is confined almost completely to the cortex on one side of the active region (the medial side) and is absent on the other side (lateral occipital cortex), which is largely unresponsive to simple visual stimuli such as gratings. This suggests that negative BOLD occurs in unstimulated parts of responsive visual areas (V1–V3) rather than in whatever cortex surrounds the active region. This argues against blood stealing and in favor of something more purposive.

In the left (ipsilateral) hemisphere (Fig. 2c), there is very little positive BOLD, reflecting the fact that receptive fields in the early visual areas are small and do not extend far into ipsilateral cortex. Extensive negative BOLD is again evident. Because there is so little positive BOLD in this hemisphere, the negative BOLD is presumably associated with activity in the opposite hemisphere and so cannot reflect blood stealing.

Group Analysis

Although the negative BOLD seems pervasive in Figure 2, it must be remembered that a liberal threshold ($P < 0.01$ per voxel) has been employed. If a correction for multiple comparisons is applied, many voxels no longer reach statistical significance. This is the case in all our subjects; thus, it is difficult to demonstrate statistical significance in individual data. A group analysis was therefore carried out, using *SPM2*. Each brain was spatially normalized to a standard template brain using *SPM2* and the activation was then averaged across the five subjects.

Figure 3 shows the results of the group analysis for all three stimulus eccentricities in the form of SPM maximum intensity projections. Data are thresholded at $P < 0.001$. Results for positive BOLD (yellow) and negative BOLD (blue) are shown in separate rows. The yellow panels show that, near the occipital pole, positive BOLD is essentially confined to contralateral cortex for all three stimulus eccentricities. The V5 complex, which is located more laterally, shows clear ipsilateral activity, as demonstrated previously [Tootell et al. 1998b]. The blue panels show extensive, statistically significant negative BOLD. Overall, this is about equally strong in the two hemispheres (stronger contralaterally at 1° eccentricity, stronger ipsilaterally at 2° eccentricity, and about equal at 4° eccentricity). It is particularly strong near the medial surfaces of the hemispheres and extends over a considerable distance in the dorsal-ventral axis, suggesting that it extends beyond V1.

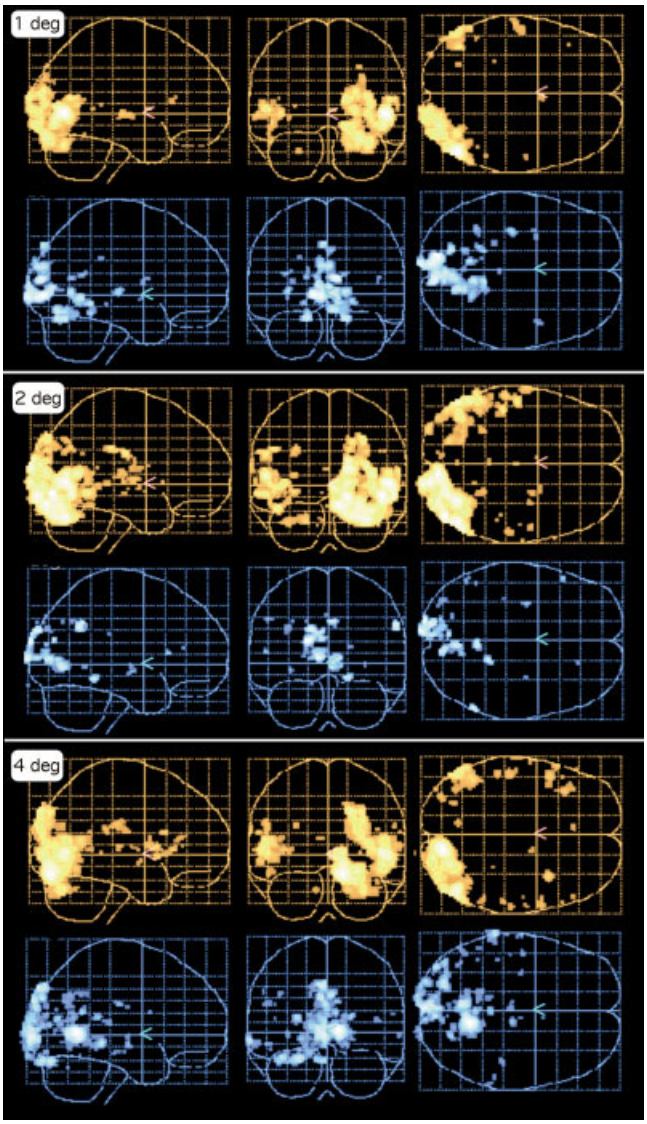

Figure 3.
Result of the group analysis. Activation averaged across five subjects shown in the form of maximum intensity projections for each stimulus eccentricity. Data points reflect voxels with a t value exceeding a threshold corresponding to $P = 0.001$ (uncorrected). Positive and negative t values, reflecting positive and negative BOLD, are shown separately in yellow and blue, respectively.

Comparison of Visual Areas

In the three observers for whom retinotopic maps were available, negative BOLD was quantified separately in each of the visual areas V1, V2, and V3. In each hemisphere, a

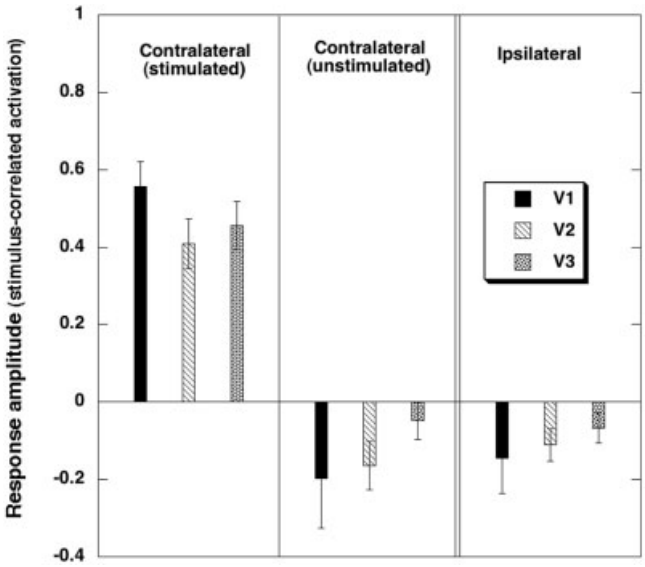

Figure 4.

Mean results averaged across six hemispheres in three brains. Results are shown for the stimulated and unstimulated zones of contralateral hemisphere (left and center) and for the ipsilateral hemisphere (right). In each case, activation is shown separately for V1, V2, and V3. Error bars = ±1 SEM.

region of interest was defined consisting of the whole of V1. Similar regions representing V2d, V2v, V3d, and V3v (VP) were also defined. These regions of interest were then subdivided into those areas representing the stimulated regions of the visual field and those representing unstimulated regions. The mean BOLD amplitude of all the voxels contained within each region was then calculated. This was done for each stimulus condition.

Figure 4 shows the results of this analysis. The data from V2d and V2v are averaged, as are those for V3d and V3v. Results are shown separately for the contralateral and ipsilateral hemispheres. In the case of the ipsilateral hemisphere (right), where there is no response to the stimulus in the early visual areas, the data simply reflect the average of the entire visual area. For the contralateral hemisphere (left and center), the results are divided into stimulated (corresponding to the region directly activated by the stimulus) and unstimulated zones. The plot reflects the mean results from all three stimulus eccentricities.

The foveal contralateral response is large and positive in all three visual areas measured, as expected. In peripheral contralateral cortex, negative BOLD is seen in all three visual areas. In ipsilateral cortex, Figure 4 shows negative BOLD, which is similar in magnitude to that in peripheral contralateral cortex.

For each visual area (V1, V2, and V3) in each observer, the deviation from zero of the mean activation of all voxels in the region of interest was tested for statistical significance, by *t*-test. Table I shows, for V1 only, the probability values associated with each of the three regions of interest, for each stimulus location in each subject. The probabilities may be slightly underestimated because of the use of spatial smoothing.

The activation is significantly different from zero in almost every case. The original observation of negative BOLD adjacent to the representation of the stimulus is thus confirmed. Moreover, the results show again that negative BOLD does occur in the non-stimulated (ipsilateral) hemisphere. Similar results were obtained for V2 and V3.

Figure 4 suggests that the observed negative BOLD is greatest in V1, in accord with our original impressions [Smith et al., 2000] and with Figure 2. This is true for both the contralateral (peripheral) and ipsilateral regions of interest. To test the reliability of this observation, one-way analysis of variance was conducted for each region of the three regions of interest in Table I, in each subject. The effect of visual area reached statistical significance in only a few isolated cases, indicating that the observed effect of visual area, although suggestive, is not statistically reliable in our data.

DISCUSSION

We found that when the visual areas of one cerebral hemisphere are activated by a stimulus, negative BOLD is seen in the other hemisphere. This is in accord with earlier indications [Tootell et al., 1998b] and provides compelling evidence that negative BOLD does not occur because of reduced local blood pressure arising from nearby capillary

TABLE I. Probability of a false positive for the three regions of interest in V1

Eccentricity (degrees)	K.S.			A.S.			A. W.		
	Contralateral			Contralateral			Contralateral		
	Stimulated	Unstimulated	Ipsilateral	Stimulated	Unstimulated	Ipsilateral	Stimulated	Unstimulated	Ipsilateral
1	<0.001	<0.05	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
2	<0.001	<0.01	<0.001	<0.001	<0.01	<0.001	<0.001	<0.001	<0.001
4	<0.001	n.s.	<0.001	<0.001	<0.001	n.s.	<0.001	n.s.	<0.001

Probability of a false positive for the three regions of interest in V1 (contralateral stimulated, contralateral unstimulated, and ipsilateral) for each stimulus eccentricity (rows) in each subject (columns). In the contralateral stimulated condition the corresponding BOLD values are all positive; for the other two conditions they are all negative. n.s., not significant.

dilation, or at least not entirely from that cause. The fact that negative BOLD is confined to the occipital cortex and is more prominent in V1 than in other visual areas suggests a purposive process related to visual processing, such as changes in visual attention.

Another possible mechanism of blood stealing needs to be considered. When one part of the cortex has high metabolic demands, it might be that flow is actively restricted elsewhere to ensure an adequate supply. It has long been known that noradrenergic neurons of the autonomic nervous system innervate cerebral blood vessels [Donath, 1968; Raichle et al., 1975]. More recently, corrosion cast studies, in which the vascular system is filled with resin and the surrounding tissue is then dissolved, have shown that the human cerebral cortex has pericytes around the capillaries and smooth muscle cells around arterioles [Rodriguez-Baeza et al., 1998]. In chinchillas, smooth muscle has been found surrounding capillaries [Harrison et al., 2002]. These systems seem to provide a means of neural control of blood flow. Electrical stimulation has been shown to cause dilation, both in capillaries and arterioles, in rat cerebellum [Iadecola et al., 1997]. The neural control of these systems is not well understood, but there is evidence that not only noradrenergic but also serotoninergic [Reinhard et al., 1979], cholinergic [Vaucher and Hamel, 1995], and dopaminergic [Krimer et al., 1998] systems innervate the vasculature and could be involved in control of blood flow. Fast local mechanisms involving glutamate have also been implicated [Attwell and Iadecola, 2002; Fergus and Lee, 1997].

If negative BOLD reflects neurally controlled constriction of vessels, rather than occurring because of local pressure changes, then it could occur at sites that are remote from the active area and even in the opposite hemisphere. We know of no evidence that this occurs, but there does seem to be a highly developed neural system for controlling blood flow that could be used for this purpose. If such a mechanism exists, it is best characterized as blood redistribution, or *blood sharing*, rather than blood stealing. The term stealing, which implies taking something without cooperation, is best reserved for local flow reductions that are due to reduced pressure in neighboring capillaries. Note that if blood sharing does occur then it could potentially contribute not only to negative BOLD but also to positive BOLD (because active dilation, as well as constriction, could occur). If so, a component of many reported BOLD activations could be due to purely hemodynamic changes.

The two remaining possible explanations of negative BOLD, neural suppression and active blood redistribution with no neural correlate, cannot easily be resolved using fMRI methods. The results of Shmuel et al. [2002] point to neural suppression, but the evidence is indirect. Indirect evidence of a different type comes from Vanduffel et al. [2000], who have documented attention-related variations in deoxyglucose uptake in different parts of macaque V1. When the animal attended centrally, they found a ring of suppression around the representation of the central visual field, although only in layers 4Cα and 4B. This suggests a reduction in neural activity in the magno-recipient peripheral visual field representation, compared to activity in a peripheral attention task. But direct investigation of neural activity is required. Some preliminary results obtained from experiments involving simultaneous fMRI and neurophysiologic recordings in monkey visual cortex suggest that negative BOLD is indeed associated with reductions in neural activity [Shmuel et al., 2003a]. In any case, it is difficult to see why it would be necessary to restrict blood flow in the contralateral hemisphere to ensure adequate blood supply. At present, the blood sharing interpretation therefore seems less probable than does genuine neural suppression.

The conclusion we draw is that negative BOLD effects in the visual cortex probably arise from suppression of neural activity levels, as others and we have suggested previously [Shmuel at al., 2002; Smith et al., 2000]. They might possibly result from blood flow changes that reflect remote neural control signals (blood sharing) rather than local changes in oxygen metabolism. But negative BOLD in the occipital cortex cannot be explained simply in terms of pressure-related blood flow changes resulting from nearby capillary dilation (blood stealing).

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This study has been reported previously in abstract form [Cotillon-Williams et al., 2003]. A similar result obtained with fMRI in monkey visual cortex was reported at the same meeting [Shmuel et al., 2003b].

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