On the Origin of Sustained Negative BOLD Response

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Abstract

Several brain regions exhibit a sustained Negative BOLD Response (NBR) during specific tasks, as assessed with functional magnetic resonance imaging. The origin of the NBR and the relationships between the vascular/metabolic dynamics and the underlying neural activity are highly debated. Converging evidence indicates that NBR, in human and not-human primates, can be interpreted in terms of decrease in neuronal activity under its basal level, rather than a purely vascular phenomenon. However, the scarcity of direct experimental evidence suggests caution and encourages the ongoing utilization of multimodal approaches in the investigation of this effect.

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1. Introduction

Functional Magnetic Resonance Imaging (fMRI) techniques are based on the Blood Oxygenation Level Dependent (BOLD) signal, which depends on the coupling between blood oxygenation and neural activity. In particular, the BOLD signal is produced by concurrent changes of physiological parameters that tend to increase it, such as cerebral blood flow (CBF), and those that tend to decrease it, such as blood volume (CBV) and oxygen consumption (CMRO\textsubscript{2}). The fractional changes of CBF are normally greater than the concomitant changes in CBV and CMRO\textsubscript{2}. The latter are thought to be mainly responsible for fine shaping of signal time-course, especially during transients.

Both Positive BOLD Response (PBR) and Negative BOLD Response (NBR) can be observed in different brain areas or even within the same area during specific task performance. While PBR is confidently associated with increase in activity of local neuronal circuits, the origin of the NBR and its relationship to metabolic and neural responses is debated. Different, somewhat incompatible hypotheses have been proposed to account for its occurrence:

- NBR may have a vascular origin, as the results of hemodynamic changes independent of local changes in neuronal activity.

- NBR could reflect the mismatch between neural/metabolic and vascular changes (i.e. a stationary version of the PBR initial dip), such that regions with increased neuronal activity do not receive the matched blood supply (neurovascular uncoupling during NBR).

- NBR might be induced by a reduction of neural activity under its basal level, with corresponding decrease of blood supply and CMRO\textsubscript{2} in hypoactive regions (neurovascular coupling during NBR).
2. Interpretations of Negative Bold Response

2.1. Hemodynamic origin of NBR

Passive (vascular steal) or active (vascular sharing) mechanisms were suggested as the hemodynamic counterpart of NBR. Both effects reflect a redistribution of CBF between activated areas, which experience a net increase in blood supply, and nearby cortical regions, where CBF decreases independently of any local neural change.

The vascular steal origin of NBR is based on the hypothesis that total blood flow remains constant during all conditions (Harel 2002 and references therein). Therefore, an increase of CBF in a given activated area must be accompanied by a decrease in nearby regions. Analysis of temporal dynamics of PBR and NBR either supported (Harel 2002) or discredited (Liu et al. 2011) this idea.

Alternatively, the reduction of flow underlying NBR could be related to the active constriction of vessels under the control of specific neuronal populations. Active regulation of CBF could be mediated by the action of autonomic nervous system neurons, as well as by inhibitory interneurons acting directly on blood vessels.

The simultaneous occurrence of PBR and NBR in remote regions during sensory stimulation in humans is consistent with the vascular sharing hypothesis (Liu et al. 2011). Indeed, the independent vascular trees that feed remote regions or even distinct hemispheres make the hypothesis of a passive redistribution unlikely to occur. On the other hand, the active control of CBF in remote areas would require a complex and developed neuronal system, a hypothesis that unfortunately lacks direct evidence (see Liu et al. 2011 and references therein). It should be noted that NBR often exhibits lower amplitude compared with PBR. Accordingly, the ratio $\Delta \text{BOLD}/\Delta \text{CBF}$ associated with NBR is higher than the ratio associated with PBR. This difference is also reflected in $\Delta \text{CMRO}_2/\Delta \text{CBF}$ ratio, which in the negative domain is smaller than in the positive domain (Pasley et al. 2007; Shmuel et al. 2002, 2006). These differences suggest that part of the NBR is elicited by a purely vascular effect. This is especially likely to occur in low–amplitude NBR areas immediately adjacent to strongly activated regions (Shmuel et al. 2006). Neural mechanisms, such as transcallosal inhibition, were
conversely suggested to play an important role in NBR taking place in remote regions (see Liu et al. 2011; Yuan et al. 2011 and references therein).

2.2. Neurovascular uncoupling during NBR

In negative regions an increased concentration of deoxy–hemoglobin is expected. This increase could be due to different coupling patterns between blood flow and oxygen consumption. In particular, a mismatch between CBF and CMRO$_2$ changes (e.g. an increase of metabolism disproportionately high compared to the increase of CBF) would induce a NBR in presence of increased neural activity. Albeit theoretically possible, such a mechanism was never observed in humans or non-human primates under physiological conditions.

Metabolic changes induced by neuronal activity (i.e. CMRO$_2$) were investigated both for PBR and NBR. Unfortunately, PET based CMRO$_2$ measurements are reliable only in case of increase in oxygen consumption, and CMRO$_2$ changes were investigated during NBR only indirectly, using BOLD–perfusion experiments, an approach that is highly sensitive to the assumptions made (Figure 1).

Shmuel and colleagues, using the calibrated BOLD approach on humans during visual stimulation, reported that NBR correlated with decreased CBF, both spatially and with respect to amplitude (Shmuel et al. 2002). Since negative areas were not stimulated during experiment because of their retinotopic organization, the possibility of a CMRO$_2$ increase in NBR regions was ruled out. These authors estimated that the decrease of CMRO$_2$ in NBR areas was smaller than the CBF decrease, consistent with the hypothesis that mechanisms eliciting PBR and NBR were similar.

Same conclusions were drawn by Pasley and colleagues, which studied the functional response of human visual cortex. They superimposed the visual stimulation on two different baselines (a normal resting baseline and a lower baseline elicited by a previous stimulus inducing NBR), and found that the CBF/CMRO$_2$ ratio was independent of baseline (Pasley et al. 2007). Consistent with this finding, a linear coupling between CMRO$_2$ and CBF was reported in Default Mode Network regions exhibiting NBR (Lin et al. 2011).
2.3. Decrease in Neuronal Activity and NBR

Neurovascular coupling is identified by a positive BOLD response that is usually matched to a regional increase of neuronal activity. Simultaneous measurements of BOLD and electrophysiological signals showed that both spiking, as represented by multi unit activity (MUA), and synaptic activity, revealed by local field potentials (LFP), are usually correlated to BOLD increase. However, LFP remains correlated to BOLD even in those conditions that cause an uncoupling between BOLD and spiking. Thus, PBR is thought to mainly reflect an increase of the input and of the local processing in a given area (Logothetis et al. 2001).

Several studies showed a tight coupling between PBR and NBR, both in terms of timings and amplitudes (Kastrup et al. 2008; Liu et al. 2011; Pasley et al. 2007; Shmuel et al. 2002). In particular, amplitude and duration of PBR and NBR in humans were reported to change monotonically with stimulus intensity and duration (Shmuel et al. 2002). These similarities suggest that the neural mechanisms eliciting PBR and NBR are correlated as well. However, fMRI alone is not able to establish whether the signal originates from vascular or neuronal process, or a combination of both. The relationship between different bands of neuronal activity and NBR was studied directly on healthy subjects, via combined BOLD and electrophysiological measurements, both in humans (EEG) and monkeys (microelectrodes) (Shmuel et al. 2006; Yuan et al. 2011).

Shmuel and colleagues found that the negative BOLD response in monkey striate cortex was accompanied by a decreased broadband neuronal signal (i.e. both LFP and MUA) relative to spontaneous activity (Shmuel et al. 2006). The decrease in LFP associated with the NBR was smaller than the increase associated with the PBR in the same frequency band. Moreover, there was no evidence for a better correlation between NBR and LFP (Shmuel et al. 2006), contrary to what was reported for the coupling between PBR and neuronal electrical activity (Logothetis et al. 2001). This discrepancy can be related to a different balance between excitation and inhibition within the neural microcircuits activity, in regions either directly stimulated or mainly subject to neuromodulatory input. Alternatively, it could be due to a departure from the linear relationship between LFP and MUA at high activity (Shmuel et al. 2006). Indeed, a marked uncoupling between MUA and LFP (and thus different predictive power of MUA and LFP on BOLD) is generally observed.
during PBR when MUA shows strong adaptation. This is thought to be related to inhibitory interneurons preventing pyramidal cells from firing, a mechanism that is more likely to occur during increased input.

Although NBR is probably correlated to a decrease in neuronal activity, the causality of this relationship still has to be elucidated. Neuronal activity could be forced under its basal level after any decrease in CBF becoming rate limiting for CMRO₂ and thus metabolism. However, this was experimentally ruled out by Shmuel and coworkers, who showed that the onset and peak of NBR always lagged behind the onset and peak of the reduction in neuronal activity, which occurred simultaneously with the stimulus (Shmuel et al. 2006). Moreover, the time course of the NBR could be predicted from the local time course of neuronal activity better than from the PBR time course in adjacent regions, implying that NBR is better explained by a purely neuronal than by a purely vascular origin (Shmuel et al. 2006).

The neurovascular coupling within different frequency bands of neuronal signal was investigated also in humans, though less extensively than for PBR. Partially at odds with the afore-mentioned experimental outcomes obtained in monkeys (Shmuel et al. 2006), Yuan and colleagues reported that in humans the neurovascular coupling during unilateral finger tapping is dependent on the sign of the BOLD response (Yuan et al. 2011). In particular, contralateral PBR was always correlated with a decrease of alpha and beta band power of an overlapped EEG source, and a decrease was also reported in theta and delta bands. To the contrary, ipsilateral NBR showed no significant correlation with EEG source power within alpha and beta band, while a positive correlation was found in theta and delta band, but only in the right handed group. These results suggest that the mechanisms underlying neurovascular coupling during NBR and PBR not necessarily share the same features. It should be noted, however, that the study suffers from some technical shortcoming; in particular, the region of interest were based on task–related activations, thus biasing the regional average of responses.

3. Conclusions

The current experimental evidence largely suggests that NBR is the counterpart of reduced neural activity. Nonetheless, there is still considerable controversy about the specific relationships between such reduction
and NBR. The direct extension to NBR of the neurovascular coupling assessed for PBR is made difficult by the fact that the decrease in neural activity can be related to multiple mechanisms. These include a net shift toward inhibition producing an unpredictable BOLD response, which can be region dependent and – of course – exquisitely related to the specific mechanisms mediating the vascular response. Alternatively, NBR could be reasonably explained by neural mass action if the level of recurrent excitation–inhibition in cortical microcircuits is reduced due to sustained changes of sensorial input or neuromodulation.

Moreover, several experiments manipulating the BOLD baseline in visual areas showed that BOLD changes induced by neuronal suppression are non–linear and region–specific, and do not always match the subjective perceptual state (see Wade and Rowland 2010, and references therein) or the neural signal (Maier et al. 2008). It should be also realized that attentional modulations could have a role in the mismatch between BOLD and neural signal during awareness suppression (Watanabe et al. 2011). Furthermore, the definition itself of a baseline for the BOLD signal is a nontrivial issue, as pointed out by several recent studies on the default mode network. This represents a potential major source of uncertainty in the exact characterization of neurovascular coupling during reduced neural activity, and especially during suppression. To this end, multimodal approaches, similar to those described in the present paper, appears to be prerequisite for directly assessing neural activity, BOLD signal, vascular and metabolic response.
References


Figure caption

Figure 1. The panels show measurements from 3 BOLD-perfusion experiments (from left to right Shmuel et al. 2002, Pasley et al. 2007, Lin et al. 2011). Iso–CMRO₂ solutions (ΔCMRO₂=0) are obtained using the currently available model for BOLD signal, with parametric dependence on α (Grubb’s relation between CBF and CBV), β (vessel size and magnetic field), and M (calibration of basal BOLD signal). In each panel, the normalized density of the iso–CMRO₂ solutions is obtained with an uniform sampling of the 3 parameters within the range considered in the relevant paper, and mapped in a color scale. The experimental results from the same paper are highlighted with a filled symbol.

Notably, there are some points that fall within the allowed iso–CMRO₂ curves, thereby corresponding to increase or decrease in CMRO₂, according to the chosen parameter set.

Therefore, care has to be exercised in drawing conclusion about putative changes of metabolism (and hence neuronal activity) using BOLD–perfusion strategies, especially considering the low sensitivity of this approach in the negative domain.