Sustained Negative BOLD and Blood Flow Response and its Coupling to the Positive Response in the Human Brain

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Most fMRI studies are based on the detection of a positive BOLD response (PBR). A few previous human studies indicated the existence of negatively responding voxels in brain regions remote from the focus of PBR (1, 2, and others). Recent studies in the anesthetized cat (3) and monkey (4) have demonstrated adjacent PBR and negative BOLD response (NBR). Here we demonstrate sustained (different from the "initial dip") negative BOLD response (NBR) that occurs concurrently with and is coupled to the PBR, via a mechanism that involves a reduction in blood flow (CBF) to the less demanding regions in the human brain.

Methods:

Subjects viewed flickering checkers at eccentricities of 2°-3° or 8°-12°, while fixating on a point. To obtain the baseline signal, a blank gray image was presented during the control period. A block paradigm was used (16 sec on, 21 sec off). Three para-sagittal slices in occipital cortex were imaged (GE-EPI, 7 Tesla, 1×1×3 mm, TR=.45 s). Perfusion fMRI was obtained from axial slices, by employing the FAIR sequence (TI=1.5s, 2×2×8 mm, τ=1.5s).

Results:

Fig. 1A presents the BOLD response to stimulation of central visual field. PBR (white voxels) was observed in posterior occipital cortex, as expected from previous retinotopic studies. NBR (gray voxels within the delineated ROI) was observed anteriorily. Spatially, the NBR was segregated from but adjacent to the PBR, at distances from 1-2 mm to 30 mm. The NBR was highly reproducible both temporally and spatially, within a session, across sessions of the same subject, and across all 8 subjects. The NBR was specific to the gray matter. The NBR depended on the spatial pattern of neuronal activity: shifting the stimulus from central (Fig. 1A) to peripheral (Fig. 1B) visual field changed the response within the ROI from NBR to PBR.

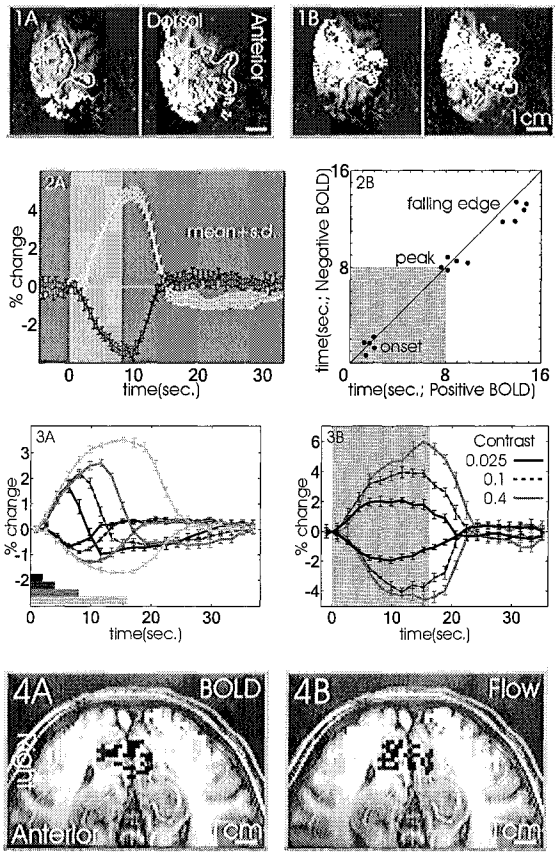
Fig. 2A presents a typical time-course. The amplitude ratio of the NBR to that of the PBR was in the range of 0.3-0.8. In phase with the post-stimulus undershoot corresponding to the PBR, a post-stimulus overshoot of the NBR was observed. The time courses of the two phenomena were similar (Fig. 2B; data from 5 subjects). The onset and time to peak of the NBR were approximately equal to those of the PBR. Consistent across subjects, the timing of the falling edge of the NBR following the stimulus offset preceded the falling edge of the PBR by approximately 1.5 sec.

The NBR and PBR were coupled to each other. The amplitudes and durations of both the NBR and PBR increased with increasing stimulus durations (Fig. 3A). In addition, the amplitudes of the NBR and PBR increased monotonically with exponentially increasing stimulus contrast (Fig. 3B).

To investigate the mechanism corresponding to the phenomenon, we combined perfusion fMRI together with independent scans of BOLD imaging from the same session (Fig. 4). The spatial pattern of decrease /increase in blood flow was correlated to the pattern of NBR (dark voxels) and PBR (white voxels) respectively.

Conclusions and Discussion:

1) Robust sustained NBR does exist in the human brain. 2) The NBR depends on the spatial pattern of neuronal activity. 3) The similarity of time-courses indicates that the mechanisms of the NBR and PBR are related in terms of changes in CBF and CBV. 4) Using the paradigm of partial visual field stimulation, neurons in the non-stimulated regions do not increase their activity. Thus, the NBR here is the result of a decrease in flow rather than increase in oxygen consumption. 5) The negative and positive responses are intimately coupled. 6) The demonstrated coupling suggests an origin of the NBR which is either a. haemo-dynamic: a passive or active redirection of blood flow from the less demanding areas *due to* the increase in flow to the more demanding areas; or b. neuronal: lateral suppression of electrical activity induced by the increase in spike activity in the active regions; the suppression might cause an active reduction in blood flow to the suppressed regions; or c. a combination of both. 7) Findings that support the existence of a major haemodynamic component in the NBR: a. NBR in remote regions within lower visual areas, at an extent not reached by the horizontal connections. b. The difference in the timing of the falling edges (Fig. 2B) is consistent with a model in which the PBR is the result of increase in CBF accompanied by increase in CMRO2, while the NBR is the result of decrease in CBF with no changes in CMRO2. 8) We cannot rule out a contribution to the NBR of neuronal suppression that may cause an active reduction in blood flow.



References:

1) Le Bihan et al., ISMRM 1995. 2) Shulman et al., JCNS 1997. 3) Harel et al., ISMRM 2001. 4) Logothetis et al., SFN 2000; HBM 2001.

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