The post-stimulation undershoot in BOLD fMRI of human brain is not caused by elevated cerebral blood volume

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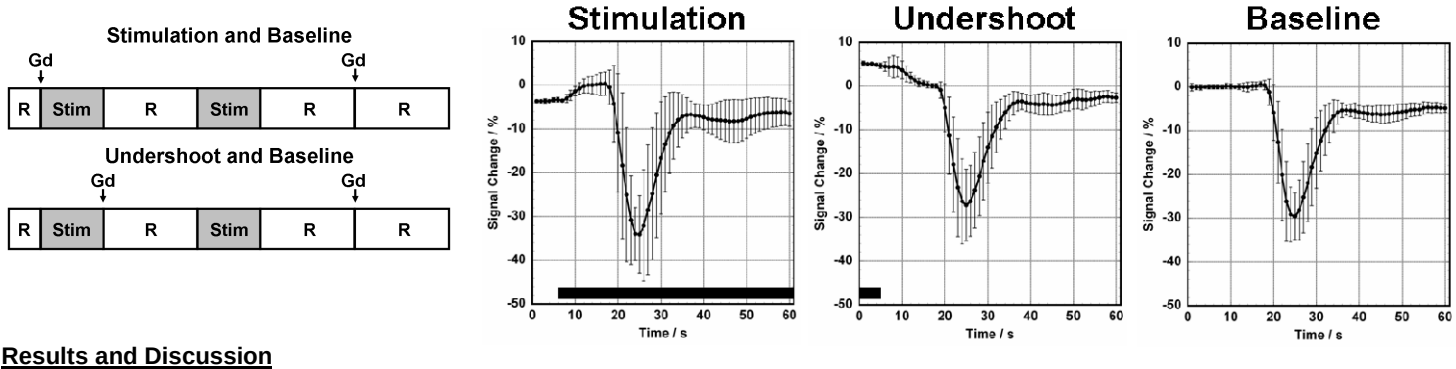
Introduction

BOLD fMRI responses to a functional challenge are caused by a dynamic interplay of altered cerebral blood flow (CBF), cerebral blood volume (CBV), and oxidative metabolism ($CMRO_2$). One of the characteristics of the BOLD response is the post-stimulation undershoot, i.e. increased deoxyhemoglobin, which has been suggested to originate from a delayed recovery of elevated $CMRO_2$ [1] or CBV [2]. To investigate the CBV contribution in humans we performed bolus-tracking fMRI using a paramagnetic contrast agent at 3 T. Relative CBV (rCBV) values were determined during either visual stimulation or the post-stimulation undershoot.

Methods

Subjects. Eight human adults (24.9 ± 4.0 years, 5 males) with normal or corrected-to-normal vision and no history of neurological or psychiatric disease participated in the study which was approved by the Ethical Committee of the University of Göttingen. – *Stimulation.* A black-white radial checkerboard (8 Hz, Stim = 2 min) was contrasted with a black screen (R = 3 min, see left Figure). First, individual hemodynamic response properties were assessed using BOLD fMRI without contrast agent. For the investigation of putative rCBV changes 8 ml of 0.5 mmol/ml Gd-DTPA (Magnevist, Schering, Berlin, Germany) followed by 15 ml 0.9 % NaCl (DeltaSelect, Pfullingen, Germany) were injected intravenously at 4 ml/s using a power injector (Spectris Solaris EP, Medrad, Warrendale, USA). In two separate experiments, the contrast agent was injected either at the onset of stimulation or at its end as well as in the final rest period. – *MRI.* All experiments were performed at 3 T (Siemens Magnetom Trio, Erlangen, Germany) using an eight-channel phased-array headcoil. For fMRI a T2*-sensitive gradient-echo echoplanar imaging technique with an in-plane resolution of 2×2 mm² was used (TR/TE = 1000/36 ms, flip angle 50°, 10 consecutive sections of 4 mm thickness parallel to the calcarine fissure). – *CBV analysis.* rCBV levels in an occipital gray matter ROI (activated during BOLD fMRI) were corrected for any unspecific effects by using data from two ROIs in non-activated frontal gray and white matter. Data processing followed previously reported procedures as closely as possible [3-5].



Results and Discussion

After the onset of stimulation, the group-averaged fMRI signal intensity in occipital gray matter (panels in right Figure) increased due to the BOLD effect, reached a rather stable level, and became severely attenuated by the inflow of the contrast agent. After the end of stimulation, the BOLD signal intensity decreased before the contrast agent caused a severe signal reduction which exactly matched the delayed occurrence of the maximum undershoot, i.e. 19.3 ± 5.1 s after stimulation. Calculation of the corresponding rCBV changes revealed a mean increase of 31.4 ± 8.6 % during stimulation, but no effect, i.e. 0.7 ± 7.2 %, in the post-stimulation undershoot phase.

These results are in excellent agreement with other human fMRI studies using the VASO technique [6-8] or near-infrared optical spectroscopy [9-11] indicating a normalized CBV during the post-stimulation undershoot phase. Nevertheless, the experimental facts in humans are opposed by a large number of animal studies using blood-pool contrast agents that suggest a delayed recovery of CBV relative to CBF after the end of stimulation, e.g. see [12,13]. Possible reasons for these discrepancies remain speculative but may include (i) inter-species differences with respect to structure and function/regulation of the microvasculature, (ii) the need for anesthesia and putative interactions with neural activity, neurovascular coupling/regulation, or even a direct vasoactivity, and (iii) the use of long-lasting blood-pool contrast agents with potentially unknown physiologic properties.

In view of the reliability of the bolus-tracking method in routine clinical settings, the present data provide firm evidence against a major if not any positive rCBV contribution to the post-stimulation BOLD fMRI undershoot commonly observed in human brain. It may be concluded that – under the assumption of a rapid normalization of CBF shortly after stimulus cessation – the undershoot is most likely attributed to prolonged oxidative metabolism. This interpretation lends support to the notion of a transient uncoupling of blood flow and oxidative glucose consumption – at least in the non-steady-state situation after a functional challenge of the human visual cortex.

References

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