The BOLD fMRI post-stimulation undershoot in human primary motor cortex is not caused by elevated CBV

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Introduction

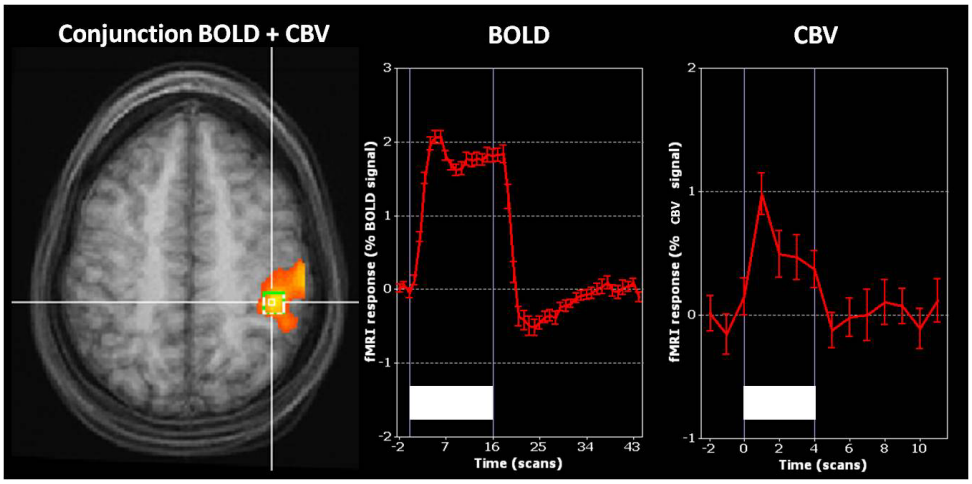
BOLD fMRI responses to a functional challenge are caused by a dynamic interplay of altered cerebral blood flow (CBF), blood volume (CBV), and oxidative metabolism ($CMRO_2$). One of the characteristics of the BOLD response is the post-stimulation undershoot, which has been suggested to originate from a delayed recovery of elevated $CMRO_2$ [Frahm 1996] or CBV [Buxton 1998]. Recently, we have shown in humans using two independent contrast-enhanced fMRI techniques that CBV normalizes rapidly after the end of stimulation in the primary visual cortex [Dechent 2010; Frahm 2008]. However, the results from contrast-enhanced CBV experiments in humans and animals are controversial, with animal studies observing elevated CBV values after the end of stimulation [e.g., Mandeville 1999]. These discrepancies might be due to inter-species differences, anaesthesia, or the cortical system investigated. Human studies mostly targeted the visual system, whereas in anaesthetized animals the somatosensory system is preferred because of technical reasons. Here, we investigated the CBV contribution to the post-stimulation undershoot in human primary motor cortex using a recently validated dynamic T1-weighted (T1w) fMRI technique based on a blood-pool contrast agent (CA) [Dechent 2010].

Methods

Four human adults (24.5 ± 2.5 years) with no history of neurological or psychiatric illness participated in the study, which was approved by the local ethics committee. All experiments were performed at 3 T (Magnetom TIM Trio, Siemens Healthcare, Erlangen, Germany) using an eight-channel phased-array head coil. First, a T1w anatomical dataset at 1 mm³ was acquired (3D Turbo FLASH). Subjects were asked to perform a sequential finger-to-thumb opposition task (~3 Hz; 32 s) interleaved with motor rest periods (56 s). Secondly, hemodynamic response properties in motor cortex were assessed using BOLD fMRI without CA (T2*w EPI: TR/TE = 2000/36 ms, 70°, 2 × 2 × 4 mm³, 22 sections, axial orientation). For the investigation of putative CBV changes a T1w 3D FLASH technique optimized to detect signal alterations related to T1 changes was used (TR/TE = 8000/3.1 ms per volume, 50°, 3 × 3 × 5 mm³, 24 sections, coronal orientation) as described [Dechent 2010]. This T1w fMRI technique was applied before CA injection – to ensure that the images were not confounded by residual CBF effects (e.g., due to inflow) – as well as after intravenous injection of the blood-pool CA (0.03 mmol/kg body weight, Vasovist, Schering, Berlin, Germany).
Group analysis was performed using the general linear model implemented in BrainVoyagerQX (Brain Innovation, Maastricht, The Netherlands). Functional raw data were motion-corrected, co-registered to the individual anatomy, and subsequently transformed into Talairach space. The stimulation protocol was either convolved with the standard hemodynamic response function (for EPI to evaluate BOLD changes) or simply shifted by one volume (8 s, for 3D FLASH to evaluate CBV changes). Activation maps were overlaid onto the averaged anatomical dataset. Time-locked averaged signal intensity time courses were extracted from a region-of-interest in the primary motor cortex.

Results

Using BOLD fMRI as well as T1w fMRI after CA administration, the motor task resulted in activation in the primary motor cortex (**Figure, left**). T1w fMRI before CA administration resulted in no detectable movement-related signal changes. The extracted BOLD signal (**Figure, middle**) revealed a positive signal change during finger movement (~ 2.1 % after 12 s) and a post-stimulation under-shoot (~ – 0.5 % after 16 s). The corresponding T1w fMRI signal after CA injection (**Figure, right**) revealed a positive signal change during finger movement (~ 1.0 % after 8 s). However, after the end of the motor task the signal rapidly normalized and was at baseline level after 16 s.



Thus, the contrast-enhanced dynamic T1w 3D FLASH technique [Dechent 2010] allowed us to monitor finger movement-induced changes of CBV in the human primary motor cortex. While we found positive BOLD as well as T1w fMRI signal changes during the motor task, the post-stimulation undershoot observable with BOLD fMRI was not accompanied by an elevated CBV signal in T1w fMRI.

Discussion

The present results from the human primary motor cortex indicating normalized CBV during the post-stimulation undershoot are in excellent agreement with previous findings for the human visual system [e.g., Lu 2004; Schroeter 2006] including our own contrast-enhanced fMRI studies [Dechent 2010, Frahm 2008]. In view of opposing animal studies that suggest a delayed recovery of CBV after the end of stimulation [e.g., Mandeville 1999], this work provides evidence against the assumption that the specific cortical system investigated (e.g., the visual or motor cortex) might be responsible for these discrepant findings. Therefore, inter-species differences and/or anesthesia in animal experiments are more likely remaining explanations.
These findings add to the mounting evidence against a positive CBV contribution to the post-stimulation BOLD fMRI undershoot in human brain. It may be concluded that, under the assumption of a rapid normalization of CBF after stimulus cessation, the undershoot is most likely attributed to prolonged oxidative metabolism.

References

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