Do differences in BOLD and CBV responses to cortical stimulation during mGluR5 blockade reflect regional differences in neurovascular coupling mechanisms?

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Introduction:

Changes in neuronal activity induce local changes in both metabolism and cerebral perfusion. Although this concept is well established, we remain uncertain of the mechanisms by which neuronal activity and the associated haemodynamic and metabolic responses are coupled[1]. Understanding these coupling mechanisms has become critically important with the growing use of functional imaging methods, such as PET and fMRI, in both basic and clinical neuroscience. It has recently been proposed that the neurotransmitter glutamate may mediate neurovascular coupling via a metabotropic glutamate type 5 (mGlu5) receptor-mediated pathway in astrocytes[2-3]. However, much of the experimental support for this proposal comes from *in vitro* studies, and the relative importance of this pathway under physiological conditions *in vivo* remains uncertain. Moreover, it is clear that expression of the enzymes in this pathway are not regionally homogenous. However, where *in vivo* studies have been performed they have largely been limited to the cerebral cortex, and the possibility of regional differences in neurovascular coupling mechanisms has received little attention. We have previously demonstrated the effect of MPEP, an mGluR5 antagonist, on the BOLD response in several cortical and subcortical brain regions during direct electrical stimulation of the rat brain[4]. Given the complexity of the BOLD response and the underlying parameters, we now determine the effect of this antagonist, under identical conditions, on the vascular response *per se* using cerebral blood volume (CBV) fMRI.

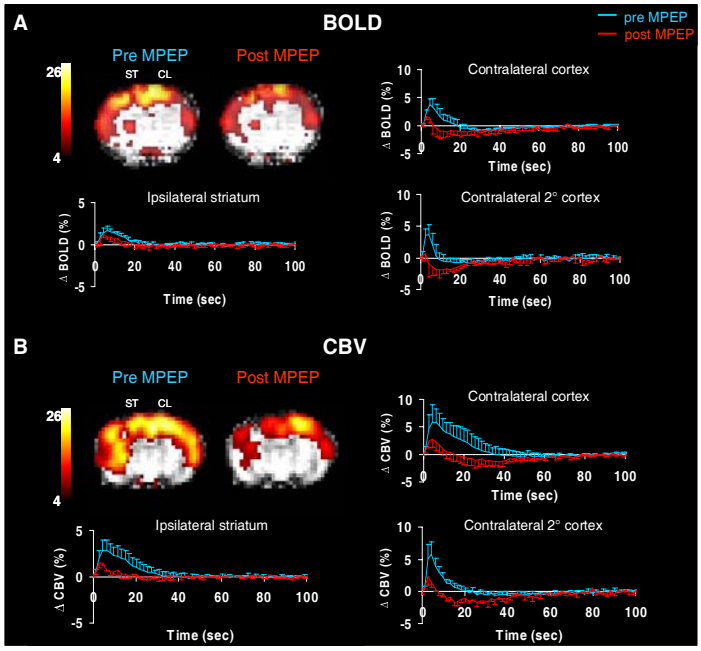
Methods:

Male Sprague Dawley rats (200-250g) were anaesthetised with halothane, artificially ventilated and physiologically monitored. A pair of fine carbon fibre electrodes were used to unilaterally stimulate the left hindpaw motor cortex. MRI was performed on a 7T horizontal bore magnet. T_2^*-weighted images were acquired using a FLASH gradient echo sequence to obtain BOLD fMRI data (TE=12ms, TR=20.5sec; 10 blocks of 2.5sec stimulation and 102.5sec rest). CBV fMRI data sets were acquired, using a long half-life iron oxide contrast agent (Sinerem, Guerbet) and the same imaging paradigm as above except TE=8ms. Either BOLD or CBV datasets were acquired before and 20min after administration of MPEP (25mg/kg i.p.) or saline (n=5 per group). Threshold statistical maps were generated using IRVA analysis from FEAT (www.fmrib.ox.ac.uk).

Results:

Similar BOLD and CBV responses to stimulation were observed in the stimulated (ST) and contralateral (CL) motor cortices, both secondary somatosensory cortices and ipsilateral striatum (see Figure). A clear reduction in the spatial extent of both the BOLD and CBV response was observed following MPEP administration in all cortical regions except the stimulated cortex (where a higher degree of variability was apparent). Similarly, the time course data show a reduction in both BOLD and CBV cortical responses to stimulation following MPEP, with a reversal of the BOLD response (and almost complete elimination of the CBV response) in the contralateral cortical regions. In contrast, in the ipsilateral striatum the time course BOLD response was only slightly, and non-significantly, reduced post-MPEP (paired t tests, P=0.17; Fig. A), whilst the CBV response in this region was significantly reduced (paired t tests, P=0.046; Fig. B). Similarly, the reduction in spatial extent of the BOLD response in the ipsilateral striatum post-MPEP did not reach significance (paired t tests, P=0.14), whilst the spatial extent of the CBV response in this area was greatly reduced post-MPEP (paired t tests, P=0.017). In control animals no significant differences in either the spatial extent or time course responses were found pre- vs. post-saline injection.

Thus, there appear to be regional differences in the relative changes in the BOLD and CBV responses post-MPEP: the ratio of CBV/BOLD decrease in peak response post-MPEP in the contralateral primary and secondary cortices is ~0.8, whilst that of the ipsilateral striatum is ~1.6.



Discussion:

We have investigated the role of glutamate as a mediator of neurovascular coupling during direct cortical stimulation of the rat brain. The largely negative BOLD response observed post-MPEP in the contralateral hemisphere is most likely attributable to a lack of vascular response in the presence of an unchanged metabolic load, indicating uncoupling of the neuronal and vascular responses. This is supported by the greatly reduced CBV response in these regions. In contrast, the BOLD response in the ipsilateral striatum appeared to be affected to a much lesser degree by MPEP administration, despite a substantial reduction in the CBV response in this area. Our findings suggest that the mGlu5 pathway plays a major role in neurovascular coupling in the cortex, but the contribution of this pathway to coupling in the striatum remains unclear. Functional imaging responses are often compared across multiple brain regions assuming a constant relationship between neuronal, haemodynamic and metabolic processes. However, there is no premise for this assumption particularly across regions with disparate neuronal architecture. The current findings indicate a lack of consistency in the relationship between CBV and BOLD (and by inference CBF) across different regions of the brain under this experimental paradigm. Thus, BOLD responses in different areas of the brain may not reflect the same underlying neuronal, metabolic and haemodynamic events.

References: **(1)** Bonvento *et al* (2002) *Trends Neurosci*, 25: 359-64. **(2)** Zonta *et al* (2003) *Nat Neurosci*, 6: 43-50. **(3)** Takano *et al* (2006) *Nat Neurosci*, 9: 260-7. **(4)** Austin *et al* (2004) *ISMRM Proceedings* 645.