fMRI Investigation of Glutamatergic Neurovascular Coupling in the Rat Brain

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Introduction: There has been increasing interest in investigating the relationship between the vascular response, as measured indirectly in BOLD imaging, and the underlying neuronal activity. Recently, glutamate itself has been suggested to be a mediator of neurovascular coupling, potentially via an astrocytic mechanism[1, 2]. Here, we investigate the effect of MPEP, an antagonist at the astrocytic metabotropic glutamate receptor (mGlu5), on the BOLD response in several brain regions during direct cortical stimulation of the rodent brain[3].

Methods: Male Sprague Dawley rats (n=4; 225 ± 27g) were anaesthetised with halothane, artificially ventilated and their physiology monitored throughout. A pair of fine carbon fibre electrodes was used to unilaterally stimulate the left hindpaw motor cortex[3]. Imaging was performed on a 7 Tesla 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). fMRI data was acquired before and 20min after 25mg/kg intraperitoneal administration of MPEP. Threshold statistical maps were generated using IRVA analysis from FEAT[4].

Results: fMRI activation was observed in both the stimulated and contralateral motor cortices, secondary somatosensory cortices and ipsilateral striatum at the stimulation amplitude used (2.33 ± 0.10mA). A reduction in the spatial extent of the response was observed in all animals following MPEP administration (Fig. 1). The BOLD time-courses in the motor and secondary somatosensory cortices (SSCs) indicated the response was greatly reduced following MPEP administration, and in the contralateral structures it became predominantly negative (Fig. 2). Nevertheless, in the ipsilateral striatum the BOLD response was well preserved.

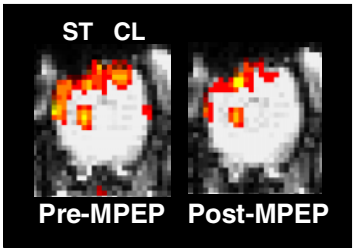

Fig 1. (above): *Threshold z-score statistical maps demonstrating activation in the stimulated (ST) and contralateral (CL) motor cortices, secondary somatosensory cortices and ipsilateral striatum in a representative rat, before and after 25mg/kg i.p. MPEP.*

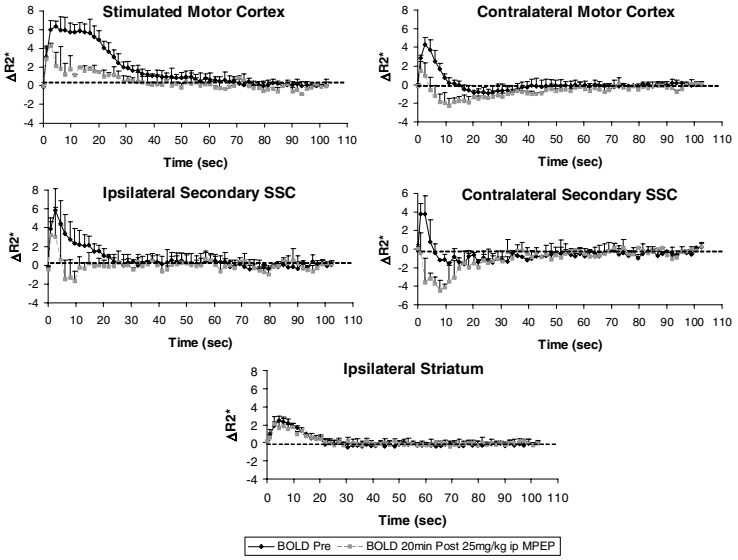

Fig 2. (right): *Averaged BOLD time-courses for the stimulated and contralateral motor cortices, secondary somatosensory cortices (SSCs) and ipsilateral striatum for all animals (mean ± SD) before and after 25mg/kg i.p. MPEP (stimulation for 2.5sec per block).*

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 response observed in the contralateral structures is most likely attributable to when there is no up-regulation of blood flow in the presence of an unchanged metabolic load. This would suggest that the predominant coupling mechanism in these structures may be via glutamate. In contrast, in the stimulated motor cortex and ipsilateral secondary SSC, where only half the response was lost, it appears that other coupling mechanisms are involved. This would not be surprising given the supraphysiological nature of the stimulation. Interestingly, the BOLD response remained preserved in the ipsilateral striatum, suggesting no involvement of the mGlu5 glutamate receptor pathway in striatal neurovascular coupling. This may reflect predominance of other pathways in the striatum, where mediator systems such as nitrous oxide, adenosine and other neurotransmitters may dominate.

The direct cortical stimulation model provides an ideal platform for investigating neurovascular coupling as activation can be detected in several functionally connected but anatomically distinct regions. This enables different pathways and mechanisms of neurovascular coupling to be investigated.

References: **(1)** Bonvento *et al* (2002) *Trends Neurosci*; **25**(7): 359-64; **(2)** Zonta *et al* (2003) *Nat Neurosci*; **6**(1): 43-50; **(3)** Austin *et al* (2003) *Mag Res Med*; **49**(5): 838-847; **(4)** www.fmrib.ox.ac.uk

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