SUBCORTICAL AND CORTICAL DISTRIBUTION OF BOLD SIGNAL FROM SOMATOSENSORY STIMULATION IN ANAESTHETISED RATS

Diana Cash[1], Tobias C Wood[1], Camilla Simmons[1], Aisling L Dixon[1], Steve CR Williams[1], and Michel B Mesquita[1]
[1]*Neuroimaging, King's College, Institute of Psychiatry, London, United Kingdom*

Introduction

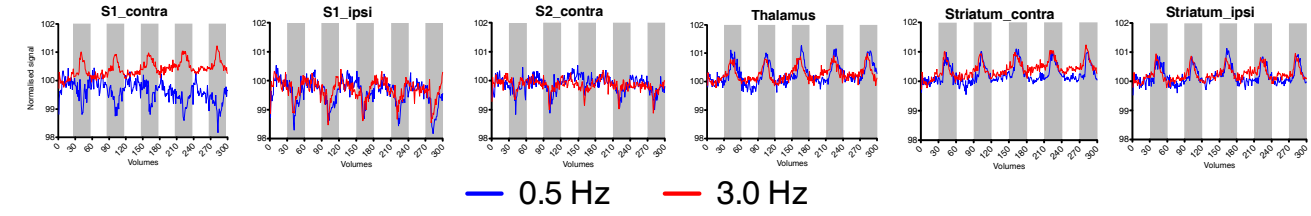
Electrical stimulation of the forepaw in rats causes increased BOLD response in the primary S1 somatosensory (forepaw) cortex over a range of stimulation strengths and frequencies. α-chloralose (α-chl) is a commonly used anaesthetic as it is particularly effective in preserving the neurovascular coupling, which forms the basis of BOLD signal. However, BOLD response under α-chl anaesthesia is observed in a small range of relatively low frequencies of (1-3Hz)[1]. Moreover, stimulation-induced BOLD usually presents in the cortex, with subcortical changes seldom reported. In this paper we show the results of sensory (electrical forepaw) stimulation in α-chl-anaesthetised rats at both the peak (3Hz) and suboptimal (0.5Hz) stimulation frequencies, as patterns of activation in the subcortical and cortical brain areas.

Methods

Total of 11 male adult SD rats were electrically stimulated (400μs duration, 2mA current, 3 or 0.5Hz) by a subcutaneous needle electrode in the left forepaw and a TENS pad under the paw. Animals were canulated under isoflurane (1.5%) anesthesia, then switched to iv α-chl 65mg/kg bolus, followed by continuous infusion at 30mg/kg/hr. **BOLD fMRI:** 7T Agilent scanner, EPI sequence, TR=1s, TE=25ms, α 90º. Each run of one frequency consisted of 300 whole brain volumes (0.5x0.5x1mm voxels, 20 slices) acquired in 5 min separated into 5 blocks of 30s 'on' and 30s 'off'. All rats received both frequencies with maximum of 10 runs per rat, and the total data set consisted of 24 x 0.5Hz and 30 x 3Hz runs. SPM8 (UCL, London) was used for pre-processing and statistical analysis: images were realigned and spatially normalised to a rat brain template; each individual rat was analysed by GLM, modelling the realignment parameters as nuisance covariate; for group analysis the individual results were analysed by one sample t test; resulting statistical parametric maps (SPM's) are group maps of significant ($p<0.05$ corrected for multiple comparisons) BOLD contrast (Fig 1 bottom left).

Results

3Hz stimulation of the forepaw elicited unilateral positive BOLD signal in the primary S1 forepaw area of the stimulated (contralateral, right) sensory cortex, but also in bilateral subcortical areas including the thalami and the striata. Surrounding the S1 positive BOLD signal were areas of apparent decrease in BOLD signal (e.g. sensory barrel field & S2). Moreover, BOLD decreases were revealed in the ipsilateral (unstimulated, left) S1 and S2 areas (Fig 1). Contrary to expectation, 0.5Hz stimulation did not result in a BOLD signal increase in contralateral S1, moreover a negative BOLD signal was apparent in *both* ipsi- and contralateral S1 (see timeseries). Elsewhere in the brain, the pattern of activation was similar between 0.5 and 3Hz, with bilateral activations in the striatal and thalamic areas, and a decrease in the ipsilateral and contralateral S2.



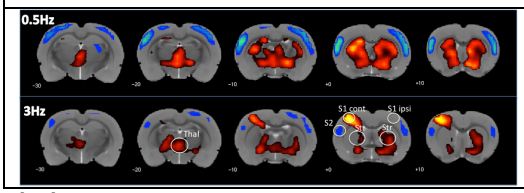


Fig 1.
TOP panel: BOLD signal timeseries from ROIs (depicted on SPMs) averaged over all rats/runs.
LEFT panel: SPMs of 0.5Hz and 3Hz in α-chl anaesthetised rat. Group maps of significant ($p<0.05$ corrected for multiple comparisons) BOLD signal increases (red-yellow) and decreases (blue-green) in BOLD contrast.

Conclusion

In cortical S1 area, a typical positive BOLD was seen at the optimum frequency of 3Hz confirming the well-known neurovascular coupling phenomenon. The immediate surrounding area showed a negative signal; this was also previously described by others[2] and attributed to either decreased neural activity or vascular steal effect. In the ipsilateral cortex, negative BOLD signal was detected in both S1 and S2 - this is probably related to the transcallosal transmission and the observed decrease in CBF reported by Devor et al[3] who also, interestingly, measured an increased glucose utilization and neural activity in the same area, thus demonstrating functional uncoupling of neural activity/metabolism and CBF. In support to this theory of uncoupled flow & metabolism under certain stimulation conditions is our observation that both GU and neural activity are increased, not decreased, by the 0.5Hz stimulation (manuscript in preparation) in the contralateral S1, whereas our BOLD response is negative (timeseries, Fig 1). Subcortical BOLD response was seen here with both frequencies. Strong thalamic activation is not surprising given that this area is a major relay of the lemniscal sensory pathway with efferents into the S1, although the significance of the apparent *bilateral* activation is not entirely clear[4]. Bilateral positive BOLD in the striatal areas is unexpected given that most studies do not report striatal activation from somatosensory stimulation in anaesthetized rodents; however this has been seen in awake rats[5]. Interestingly, the opposite response – bilateral negative BOLD, was produced by a unilateral whisker stimulation[6] and also by a unilateral noxious forepaw stimulation[7]. Given there are projections into the striatum from the cortex S1[8] as well as a direct thalamo-striatal projection[9], it is not possible to clarify the relative contribution of either connection, or to decipher the nature of this connectivity in terms of the synaptic activity from present data. Finally, the observation of a *similar* pattern of activations in the ipsilateral cortex and in subcortical areas under both stimulation frequencies, but their *divergence* in the contralateral S1, warrants further investigation.

References: 1) Hyder F (2004). Stroke 35(11 Suppl 1): 2635-2641, **2)** Shmuel A, et al. (2002). Neuron 36(6): 1195-1210, **3)** Devor A, et al. (2008). J Neurosci 28(53): 14347-14357. **4)** Cho YR, et al. (2008). J Reconstr Microsurg 24(8): 551-557. **5)** Duong TA, et al (2003). Proc. Intl. Soc. Mag. Reson. Med. 11. **6)** Mishra AM, et al. (2011). J Neurosci 31(42): 15053-15064. **7)** Shih YY, et al. (2011). J Cereb Blood Flow Metab 31(3): 832-841. **8)** Kadantseva AG, et al. (1992). Zh Evol Biokhim Fiziol 28(1): 24-30. **9)** Kamishina H, et al. (2008). Brain Res 1204: 24-39.