SIMULTANEOUS FMRI AND LONG-TERM IN VIVO ELECTROCHEMISTRY (LIVE): IDENTIFYING THE NEUROCHEMICAL CORRELATES OF FUNCTIONAL IMAGING SIGNALS

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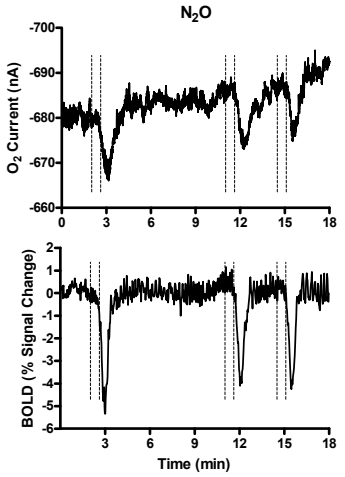
Objectives: The use of functional magnetic resonance imaging (fMRI) in both basic and clinical neuroscience is rapidly expanding. However, although advances have been made in correlating the observed signal changes to the underlying neuronal activity, the fact remains that this technique does not directly measure neuronal activity but rather associated haemodynamic (and metabolic) events. Moreover, fMRI responses are often compared across multiple brain regions assuming a constant relationship between neuronal, haemodynamic and metabolic processes, despite substantial differences in neuronal architecture. Only by fully understanding the relationship between haemodynamic, metabolic and neuronal events will we be able to realize the full potential of functional neuroimaging. In order to achieve this we must find a way of correlating fMRI data, which largely reflects the haemodynamic component, with neural and/or metabolic information. Long-term *in-vivo* electrochemistry (LIVE) enables real-time monitoring and measurement of brain metabolites[1]. In this study we have developed methods for simultaneous measurement of fMRI responses and tissue oxygen concentration via LIVE for direct correlation of metabolic and haemodynamic factors. In order to mimic changes in oxygen utilisation and supply during neuronal activation we have altered the concentration of oxygen in the inspired air. To our knowledge, this is the first report to show direct correlation of BOLD and tissue O_2 signal changes, and lays the foundation for simultaneous measurement of metabolic and fMRI responses to neuronal activation.

Methods: Carbon fibre electrodes were developed to minimise imaging artefacts: carbon fibre threads (diameter ~100μm) were attached to copper wire using conductive silver epoxy and insulated, leaving ~2.5mm exposed for insertion into the brain. Animals (n=3) were anaesthetised with 1.8% isoflurane in 70%N_2O:30%O_2, and a recording electrode implanted into the right motor cortex (Bregma -1.5mm). Two further electrodes (auxiliary and reference) were implanted in the same cortical hemisphere (Bregma +3.5 and +4.5mm). Changes in O_2 concentration were monitored using constant potential amperometry, with the electrode held at -900 mV (vs reference). A multi-echo gradient echo imaging sequence was used to obtain blood oxygenation level dependent (BOLD) fMRI data: flip angle = 20º; TR = 27.3ms; TE = 7, 14, 21ms; voxel size 0.47mm x 0.47mm x 1.5mm. Mean echo images were calculated from the arithmetic mean of the individual echo images. In one animal, CBV fMRI measurements (imaging details as for BOLD) were made following i.v. injection of 0.15ml ferumoxtran-10 (12mg Fe/kg; Sinerem®, Guerbet, France; gift from Guerbet Research). Both fMRI and voltametric data were acquired continuously. Following a baseline period of 3min, oxygen content of the inspired gases was either reduced (0% O_2) for 30sec or increased (50%, 70% or 100% O_2) for 1 min; 3 repetitions per condition.



Results: Tissue O_2 measurements and BOLD responses obtained simultaneously demonstrated close correlation during complete oxygen removal (100% N_2O) as shown in the figure (BOLD data taken from ROI in region of recording electrode). Both measurements showed a slightly delayed, but marked negative response on elimination of inspired O_2, owing to increased deoxyhaemoglobin levels (BOLD) and decreased tissue oxygen. Conversely, when the inspired oxygen was increased positive changes in both the BOLD and tissue oxygen signals were observed. Interestingly, a modest *reduction* in USPIO concentration, and hence CBV, was observed during the periods of 100% oxygen despite the positive BOLD responses measured.

Conclusions: Our findings demonstrate the practical feasibility of obtaining real-time metabolite information during fMRI acquisition. Although demonstrated here for oxygen measurements, the same LIVE technology can be applied to the measurement of many different neurochemicals opening up numerous avenues for investigating the relationship between fMRI signal changes and the underlying neurochemistry. Moreover, this work provides support for the use of LIVE monitoring of tissue oxygen concentration to predict the BOLD response under conditions that are not amenable to the magnet environment, such as in awake rats performing specific behavioural tasks. The technique thus provides a potential animal surrogate of human fMRI experimentation.

References: 1.O'Neill, R.D.,Lowry, J.P., *Voltammetry in vivo for chemical analysis of the living brain.*, in *Encyclopedia of Analytical Chemistry.* 2000, 676-709.