Fast bolus-tracking fMRI in medetomidine-sedated rats using intravascular tracer: towards quantitative fMRI

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Introduction: Gadolinium-based contrast agents have been used as intravascular tracers, and are standard experimental tools for describing relative and absolute blood volumes by the indicator dilution method (1); however, due to difficulty in determining an accurate input function, measuring blood flow with these agents is problematic (2). Using a neuronal activation paradigm recently described (3) that has potential for longitudinal studies, we show that neuronal activation can not only be easily detected using our method, but that information about the haemodynamic response can be gleaned that would be impossible to determine using blood-oxygen level-dependent (BOLD) functional magnetic resonance imaging.

Methods: MRI Images of rat primary somatosensory cortex were obtained using a 7T spectrometer (Bruker BioSpin) using purpose-built transmit and receive coils. T1-weighted images of the coronal slice of interest were acquired using a fast gradient echo sequence (TE 3.5ms, TR 11.0ms, Matrix 64x64, Resolution 0.53x0.53x1.6mm, Flip Angle 30°, NA= 1, NR = 120, Acquisition time 60s). Male Wistar rats (n=4) were placed in the scanner under sedation with a continuous subcutaneous infusion of medetomidine (3) (Domitor, Pfizer) and electrically stimulated using 5ms duration, 5Hz, 3V pulses via electrodes connected to each forepaw to bilaterally stimulate the associated cortical areas. Shortly after initiation of stimulation and during acquisition of images, a bolus of meglumine gadopentate (Magnevist, Bayer) was injected via a tail-vein. The resulting images were evaluated using a software script in IDL language (ITTVIS) and bolus moment maps and transit curves calculated for the active regions and for the cortex as a whole, the latter acting as a control.

Results: The temporal activation pattern of select cortical neurons was clearly visible on subtraction maps (Fig. 1), and regions of activations selected from these maps showed a difference in signal amplitude between activated and control regions (Fig. 2). First- and second-moment maps of the imaging slice are shown in figs 3 & 4. Although the active regions show no change in first moment compared to the control region (P=0.42 & P=0.54 for right and left respectively), the second moment was significantly different (P<0.001 for both left and right regions) between both activated regions and the control region (student's t-test).

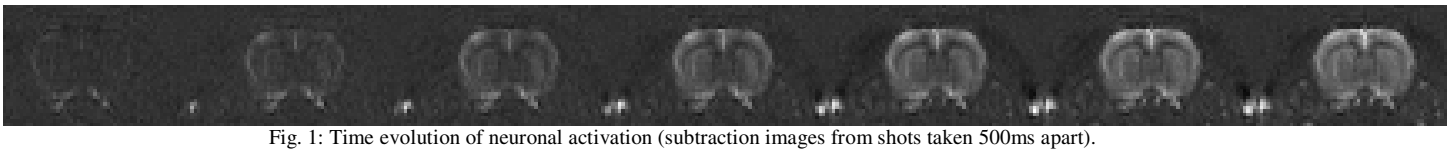


Fig. 1: Time evolution of neuronal activation (subtraction images from shots taken 500ms apart).

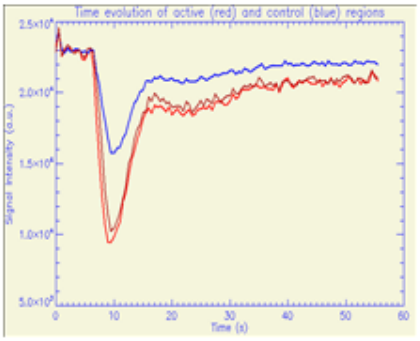
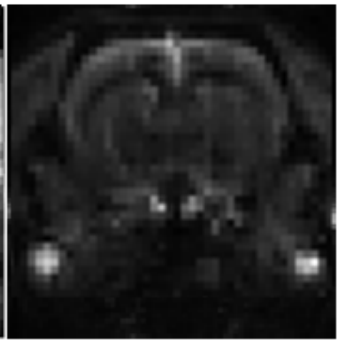


Fig. 2: Time evolution graph of active (red) and control (blue) regions

Fig. 3: 1st moment map



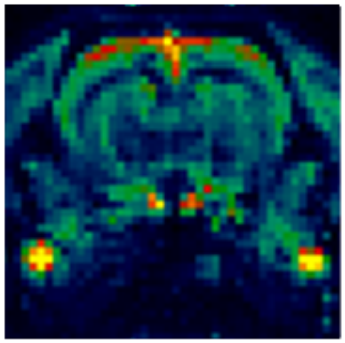


Fig. 4: 2nd moment map (also shown in pseudocolour)

Discussion: First moments of drug passage are generally thought to reflect mean transit time (MTT) through the entire vasculature, whilst the second moment has been hypothesised to represent microvascular topology (4) and this has been applied to other animal models to determine microflow heterogeneity (5). Our results show that the activation response causes a measurable increase in heterogeneity which can be characterised further due to the fine temporal resolution of our method. It does not however show a significant difference in MTT at the site of activation. This surprising result merits further investigation. Injection of intra-carotid contrast agents would provide further information, as the bolus input function could be accurately characterised, allowing accurate quantification of the haemodynamic response to activation. The method also shows promise for longitudinal studies in which changes in activation response could be repeatedly sampled over time. In conclusion, we present a novel method for both visualising neuronal activation and quantifying the associated vascular response.

References: (1) Zierler 2000 Ann Biomed Eng **28**(8):836-48. (2)Li *et al.* 2000, NeuroImage **12**: 442-452. (3)Weber *et al.* 2006, Neuroimage **29**(4):1303:10. (4) Weisskoff *et al.* 1993 Magn Res Med **29**: 553-8. (5) Tomita *el al.*2002, J Cereb Bl Fl Metab **22**:663-9.