Does vasomotion alter functional connectivity? A multi-modal study using Optical Imaging Spectroscopy and BOLD *f*MRI

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Target audience: All neurovascular coupling, functional connectivity, vasomotion, pre-clinical scientists & users of BOLD fMRI.

Purpose: Research has shown that the early onset of neurodegenerative disorders such as Alzheimer's disease can be characterized by a disturbance in functional connectivity between different brain regions[1]. Perturbations in brain connectivity are inferred by examining correlations/anti-correlations in resting state (i.e. absence of evoked neuronal responses) Blood Oxygenation Level Dependent (BOLD) functional Magnetic Resonance Imaging (*f*MRI) signals. However, the BOLD signal only reflects changes in magnetic field homogeneity caused by varying concentrations of paramagnetic deoxyhemoglobin (Hbr) in the blood stream. The haemodynamics driving the BOLD signal are drastically affected by altered neurovascular coupling or baseline physiological conditions [2]. Therefore inferring connectivity changes from the BOLD fMRI signal in diseases states, where these conditions are obviously compromised, may be problematic.

The present study examines the magnitude and spatial correlations of fluctuations in BOLD fMRI signals and underlying hemodynamics following manipulation of systemic blood pressure (BP) in anesthetized rodents; to part emulate physiological conditions in disease states. Changes in systemic BP are known to modulate 0.1Hz oscillations in the cerebral haemodynamics. Although spontaneous vasomotion oscillations have been shown to be unrelated to cardiac rhythm[3] the origin and physiological function are still debated. While some studies have shown a neural basis for the signal others have suggested it is vasogenic[4], helping optimize microcirculatory function for delivery of oxygen to the tissue[3]. If the vasomotion signal is driven by neuronal activity, modulation of the signal may reflect changes in connectivity unrelated to the pathology of a disease condition.

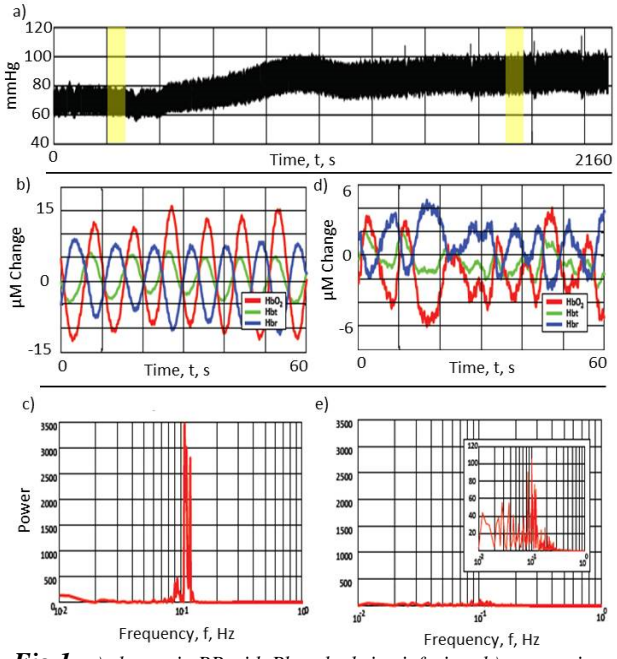

Fig 1. *a) change in BP with Phenylephrine infusion; b) vasomotion oscillations seen in low BP condition; c) Frequency power analysis; d) & e) for the normal BP condition – vasomotion damped.*

Methods: BOLD fMRI measurements were made at 7 Tesla in a small animal MRI facility (Bruker BioSpec, 310mm bore) utilizing a volume coil and 4-channel array coil for TX/RX respectively. Urethane anaesthetized animals (n=7) were artificially ventilated and cannulated for monitoring arterial BP and intravenous infusion. Application of Urethane lowers BP inducing 0.1Hz vasomotion in the brain. Phenylephrine was infused to increase BP (fig 1a) and dampen the oscillations. GE-EPI fMRI data (128*128, 1s TR) was collected continuously during the infusion. Further modulations of BP and thus vasomotion were induced by respiratory challenges. Brain connectivity maps were generated from correlation analysis of the resting state data before and after changes in BP using a seed region in the somatosensory cortex (fig 2). In a separate experiment (n=5) we investigated the underlying haemodynamics using 2D-optical imaging spectroscopy (2D-OIS). Preparation as above with the addition of a thinned skull cranial window allowing direct imaging of the cortex. 2D OIS used a switching Galvanometer using 4 λ (495, 586, 559 and 575nm) and a CCD with an effective frame rate of 8Hz for each λ. The spectral analysis was based upon the path length scaling algorithm incorporating a MR based heterogeneous tissue model. The spectral analysis produced 2D images over time, of oxy-, deoxy- and total-haemoglobin changes (HbO2, Hbr and HbT) for correlation analysis.

Results: We found

1) a robust 0.1Hz vasomotion oscillation in both BOLD fMRI and 2D-OIS measurements of the haemodynamics in the rat brain when BP was compromised (fig 1b). This was quantified with power frequency analysis (fig 1c).
2) by altering the physiological state and increasing BP by phenylephrine infusion or respiratory challenge the magnitude of the vasomotion oscillations were reduced (fig 1d&e).
3) The magnitude of vasomotion is dependent on the amount of oxygen available in the brain.
4) 3D connectivity maps generated from correlation analysis of the resting state data before and after changes in BP using a seed region in the somatosensory cortex showed clear differences (fig 2).

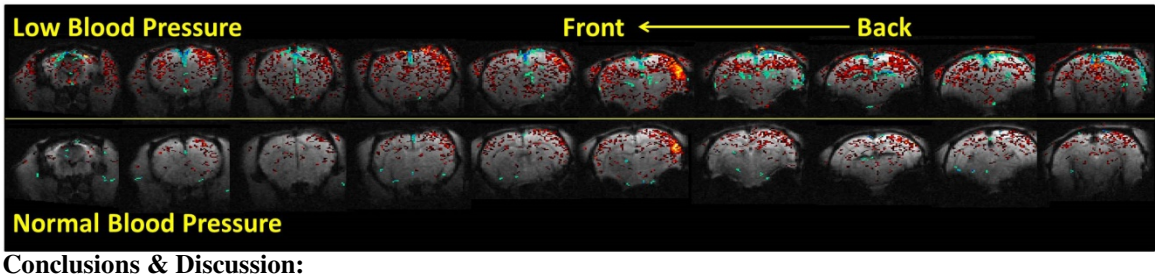

Fig 2. *Resting state BOLD fMRI functional connectivity maps based on correlation analysis before (low BP) and after (normal BP) Phenylephrine infusion.*

Conclusions & Discussion:

This study used resting state BOLD fMRI and 2D-OIS measurements to investigate perturbations in brain connectivity that occur under altered physiological states one might be presented with in the diseased patient. Changing the systemic blood pressure modulated the 0.1Hz vasomotion signal and connectivity maps before and after this change were shown to be different. Data from this pre-clinical in-vivo multimodal imaging study suggests that care should be taken when characterising the early onset of neurodegenerative disorders using functional connectivity as perturbations could simply be related to changes in physiological state.

References: 1. Wang et al. (2007) Human brain mapping (10):967-78; 2. Kennerley et.ak. (2012) JCBFM (32): 468-80; 3. Pradhan and Chakravarthy (2011) Acta Physiol (201):193-218; 4. Hudetz et.al. (1998) Advn Exp Med Bio. (454):551–559.