Sinusoidally modulated CO_2 stimulus provides new temporal information on cerebrovascular reactivity

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INTRODUCTION - Cerebrovascular reactivity (CVR) maps provide important diagnostic information in the investigation of cerebrovascular diseases, such as Moyamoya (1) and arterial steno-occlusive disease (2). Conventional methods of CVR map generation use alternating pseudo-steady state levels of $P_{ET}CO_2$ (end-tidal partial pressure of CO_2) during scanning and then overlay each voxel of the anatomical MRI image with a colour corresponding to the magnitude of BOLD signal change per mmHg change in $P_{ET}CO_2$. A limitation of this protocol is that information about the time course of the response to the CO_2 stimulus or regional delays in reactivity are lost. To address this issue, we applied a sinusoidally modulated CO_2 stimulus and used a travelling wave (Fourier transform) analysis method (3), as used for retinotopic mapping. This new technique detects correlation in tissues with arbitrary delay times and has the added benefit of allowing the phase delay between tissues to be measured.

METHOD - *MR Acquisition:* Five healthy subjects were scanned using a Philips Achieva 7.0 T equipped with a volume transmit and 16-ch SENSE receive coil. Thirty contiguous GE-EPI slices, giving whole head coverage, were acquired with $2\times2\times3mm^3$ resolution, SENSE 2, TE=25ms, TR=4s.

Stimulus Delivery: $P_{ET}O_2$ was maintained at 100mmHg and $P_{ET}CO_2$ was sinusoidally modulated between 35mmHg and 45mmHg over a 60s period for ten cycles using algorithms (4) applied by a computer-controlled gas blender and a modified sequential gas delivery breathing circuit (RespirAct™, Thornhill Research Inc., Toronto, Can.). $P_{ET}O_2$ and $P_{ET}CO_2$ were continually monitored throughout.

Analysis: Images were realigned and spatially smoothed (1.5× voxel kernel) in SPM5. MR time-courses were normalised to the mean signal and detrended (4^{th} order polynomial). A pixel-by-pixel FFT was applied. The magnitude of the effect of the stimulus was determined from the Fourier component at the stimulus frequency (a_F). The correlation value was calculated as the amplitude a_F divided by the square root of the time-series powers, a_f (Eq. [1]). The haemodynamic delay was found from the phase angle of the complex FFT value at the stimulus frequency.

$$c = \frac{a_F}{\sqrt{\sum_{f=0}^{N-1} a_f^2}} \quad [1]$$

RESULTS – Fig. 1 displays the unthresholded correlation map. High correlation values are mostly located within the GM. Fig. 2 maps the relative haemodynamic delay in seconds. Time zero was arbitrarily selected and therefore the colour-bar shows the relative time delay between different tissues. There is a clear delay between GM and WM, with a mean value of 4.5±2s (n=3). By selecting a narrower delay window (Fig. 3) it is possible to observe heterogeneity in the haemodynamic delay of GM. It is important to note that the magnitude of the correlation in Fig. 1 is not completely predicted by the magnitude of the haemodynamic delay in Fig. 2 or 3. Fig. 4 shows the mean (averaged over pixels with c>0.5) BOLD signal change (top) produced by a sinusoidal change in $P_{ET}CO_2$ (bottom).

DISCUSSION - This new approach to CVR mapping allows correlated areas to be identified regardless of the underlying haemodynamic delay. This will be useful when considering tissue viability in the presence of ischaemia where tissue may still be supplied with blood via collateral vessels, but this supply may be delayed, as such information would be missed by conventional CVR mapping methods. In this experiment only a relative haemodynamic delay was measured, but in future accurate synchronisation of the RespirAct™ and MRI systems will allow an absolute delay to be measured. This new method gives access to an important new physiological parameter that could be useful in the diagnosis and treatment planning of patients with steno-occlusive disease (2).

REFERENCES – (1) Mikulis *et al.*, J. Neurosurg., 103:347, 2005, (2) Mandell *et al.*, Stroke, 39:2021, 2008, (3) Engel *et al.*, Cereb. Cortex, 7:181, 1997, (4) Slessarev *et al.*, J. Physiol., 581:1207, 2007

Fig. 1 – Correlation map at CO_2 stimulus frequency

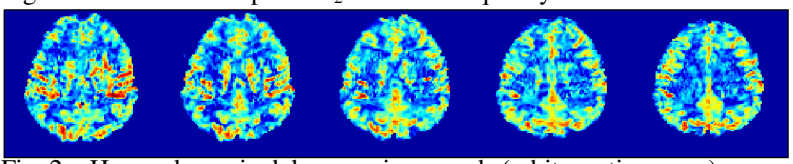


Fig. 2 – Haemodynamic delay map in seconds (arbitrary time zero)

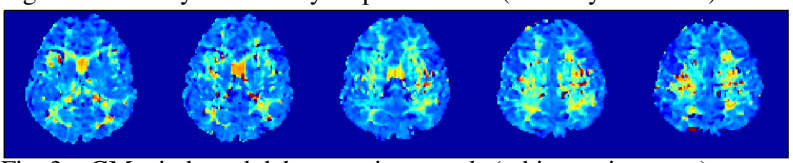
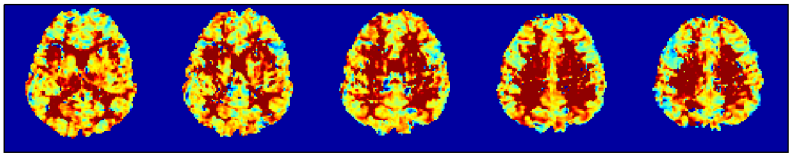


Fig. 3 – GM windowed delay map in seconds (arbitrary time zero)



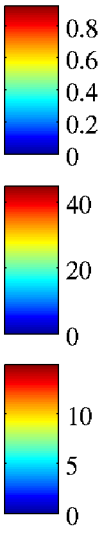


Fig. 4 – BOLD & $P_{ET}CO_2$ timecourse