The association between pulse wave velocity, as a marker of sympathetic tone, and resting state BOLD signals

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Introduction Neural activation causes a rise in cerebral blood flow (CBF) and a fall in oxygen extraction fraction leading to an increase in BOLD signal. Dynamic changes in both blood pressure and arterial CO_2 concentration lead to variations in CBF [1]. This causes fluctuations in the BOLD signal in the absence of neural activity changes obscuring signals of interest. BOLD confounds arising from fluctuations in arterial CO_2 (0-0.05Hz) [2] and changes in depth of breath (~0.03Hz) [3] can be removed. Similar BOLD noise is likely to arise from variations in blood pressure when cerebral autoregulatory processes try to maintain a steady-state CBF [4]. This is supported by evidence that changes in arterial blood pressure are synchronous with heart rate variability [5] which has been shown to correlate with resting state BOLD signals [6]. Fluctuations in arterial blood pressure are controlled by the sympathetic nervous system through changes in arterial tone [7]. Sympathetic tone may be monitored by measuring arterial stiffness through pulse wave velocity (PWV) measurement. In this study, BOLD correlates of PWV were investigated to demonstrate the influence of sympathetic tone and related blood pressure fluctuations on fMRI signals.

Methods Resting state BOLD fMRI datasets were acquired on 6 subjects (2 female) at 3T (GE HDx) using gradient-echo EPI as part of a larger study (TR=3s, TE=35ms, matrix=64x64, FOV/slice=205/3.2mm, flip=90º, 53 slices, reps=200). A T1-weighted whole-brain structural scan (1x1x1mm voxels) was also acquired. *Pulse Wave Velocity:* Partially inflated non-invasive blood pressure measurement cuffs (inflated to ~60mmHg) were placed around the left bicep and left thigh. The pressure wave from each cuff was measured at 500Hz with a separate pressure transducer connected to an ADC. The PWV time series was calculated at 1sec resolution by measuring delays between the traces in a 10sec sliding window using cross correlation and dividing the values by the arterial distance between the cuffs. *Processing:* The fMRI data were motion corrected, detrended, the time series in each slice were shifted to the same temporal origin, the resulting datasets were converted into % change values and spatially smoothed with a Gaussian filter of FWHM = 6mm. Global signals were calculated for each subject by averaging over all brain voxels. Correlation values between these signals and the corresponding PWV time series were calculated. GLM analyses were also performed on the % change datasets using each individual subjects PWV as a regressor. To investigate whether BOLD signals are delayed with respect to PWV, GLMs were performed with multiple delays at the TR resolution. Anatomical datasets were registered to the functional data and segmented into grey matter (GM), white matter (WM) and cerebral spinal fluid (CSF). Differences in the PWV/BOLD relationship for GM and WM were investigated.

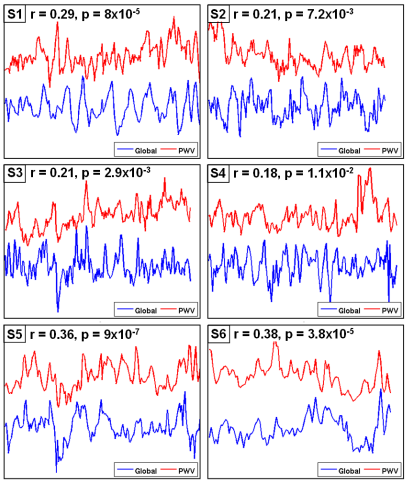

Figure 1: Plots of pulse wave velocity and global signal

Results Large significant correlations between pulse wave velocity and the global BOLD signal exist (see Figure 1). Across the subjects, PWV explains between 3% and 14% of the variance in the global signal. Cross correlation analyses demonstrate that this relationship is almost instantaneous with the delay being less than a TR (3s). The average z-statistic is significantly lower in CSF than GM masks (p=0.01), otherwise no consistent differences in the relationship between the GM, WM and CSF vs PWV correlations were found. GLM analyses show that the variance explained by the PWV is widespread throughout the brain but not necessarily consistent across subjects (Figure 2). GLMs with the PWV regressor at different lags demonstrate that the most variance is explained across the voxels when no delay is present between PWV and the BOLD signal.

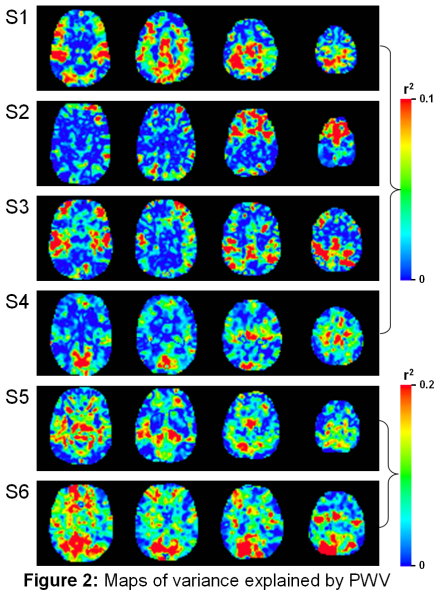

Figure 2: Maps of variance explained by PWV

Discussion This study demonstrates that significant variance in the global BOLD signal can be explained by variance in PWV measurements. The influence of pulse wave velocity on the BOLD signal is almost instantaneous as would be expected if this variance is attributed to short-term fluctuations in CBF driven by blood pressure fluctuations (i.e. cerebral autoregulation). The relationship between PWV and the BOLD signal is widespread throughout the brain. Localisation to more vascular regions is expected and may be seen in some subjects in Figure 2. However, the inherent noise in the current PWV measures makes voxel-wise comparisons difficult. Future improvements in PWV measurements will lead to improved localisation of effects. This study suggests that alterations in vascular responses to changes in blood pressure in clinical conditions could affect studies of BOLD signal connectivity. For example, in Alzheimer's patients low-frequency variability in blood pressure is enhanced, suggesting impaired arterial baroreflex function [8]. Measurement of PWV may give insight into these impairments and provide a way of removing related confounds in BOLD functional connectivity analyses.

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References: [1] Mitsis 2004 IEEE-TBE:51,1932; [2] Wise 2004 NI:21,1652; [3] Birn 2006 NI:31,1536; [4] Lagopoulos 2006 Acta Neuropsy:18,100; [5] Katura 2006 NI:31,1592; [6] Shmueli 2007 NI:38,306; [7] Failla 1999 J Hypertension:17,1117; [8] Claassen 2009 J Alzheimers Dis:17,621