Imaging the Fragile Brain: Using BOLD Signal Fluctuations to Study Perfusion in Normal Subjects and Patients with Cerebrovascular Disease

Thomas Christen[1], Deqiang Qiu[1], Wendy Ni[1], Michael Moseley[1], and Greg Zaharchuk[1]
[1]*Radiology, Stanford University, Stanford, California, United States*

Introduction: Physiological fluctuations that arise from heart rate and respiration are usually considered as noise and discarded in Resting State functional MRI. Yet, these processes also act as periodic challenges to the vascular network and therefore BOLD fluctuations should contain information about brain perfusion, vascular reactivity, and oxygenation. Only a few studies have attempted to use these signals to study tumor hypoxia [1] or stroke [2] in animals. A retrospective analysis was conducted in humans but was limited by the MR sequence used for the analysis [3]. In this work, we acquired resting state BOLD imaging in volunteers and patients to specifically study these processes. The data was analysed in two ways to create the following maps: (1) amplitude of the signal fluctuations after high pass filtering of the signal, (2) the correlation between the MR signal in major blood vessel, such as the sagittal sinus, and the rest of the brain.

Materials and Methods: The local IRB committee approved all studies. 5 normal volunteers were scanned at 3T (MR750, GE Healthcare Systems, Waukesha, WI) with an 8-channel head coil. The protocol included a 3D T1-weighted fast spoiled gradient echo sequence used to acquire high-resolution structural information of the whole brain. A gradient echo EPI sequence (TE=35ms, TR=3000ms, 35slices, FOV=20x20 cm, ST=4mm, 128x128) with 128 repetitions was used for resting state acquisitions. A multi-echo SAGE-EPI [4] sequence (TR = 1800ms, flip angle 90°, 15 slices of 5mm thickness) was used to acquire Dynamic susceptibility contrast (DSC) maps during injection of ferumoxytol (1.75 mg Fe/kg at 1 mL/s, Feraheme, AMAG Pharmaceuticals, Inc., Cambridge, MA). A stroke patient and a patient with chronic carotid occlusion were also scanned. Bolus DSC (2 min) was performed using a single-shot EPI gradient echo PWI method (TR/TE = 1800/40 ms, flip angle 60°, 0.1 mmol Gd). Resting state data were acquired with a gradient echo EPI sequence (TE=45ms, TR=1800ms, 15slices, FOV=20x20 cm, ST=5mm, 128x128) with 160 repetitions. A high spatial/temporal resolution resting state acquisition was also acquired (TR=500ms, ST=4mm, 256x256, 6slices, 300repetitions).
Data from the scanner were imported into Matlab (MathWorks Inc., Natick, MA, USA) and SPM8 was used for co-registration of the scans. Hemodynamic maps (CBF, CBV, MTT, and Tmax) were created using automatic AIF detection and circular SVD [5]. Resting state data were corrected for head motion (least squares approach, 6 parameters spatial transformation). The first ten time points were discarded to avoid transient signal changes before magnetization reached steady-state. The time series were transformed to the frequency domain with a fast Fourier transform, and the Amplitude of Signal Fluctuations (ASF) was computed as the squared root of the average of the Power spectral density >0.1Hz for each voxel (Fig.1a). For the blood vessel correlation approach, the data were spatially smoothed with a Gaussian kernel and frequency filtered over 0.1Hz. A region of interest was manually delineated over the sagittal sinus. A cross correlation analysis was performed between this 'seed' signal and all other brain voxels. The analysis was also performed with the reference signal shifted from +/-5TR to account for possible time delays. The vascular correlation maps were created by taking the maximum of the correlation coefficient over the time lag, provided the latter was higher than a confidence bound (Fig2a).

Fig.1 Amplitude of Signal Fluctuations (ASF)

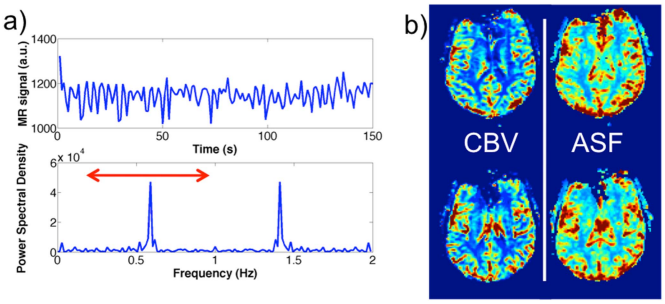
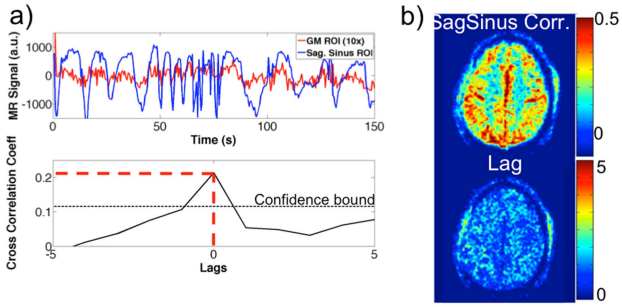
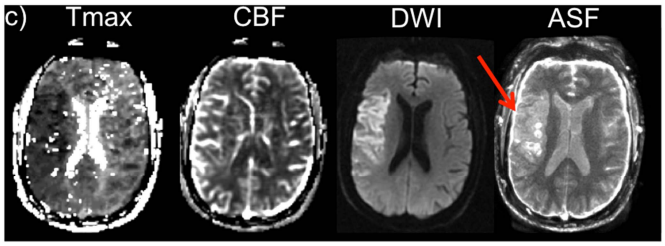
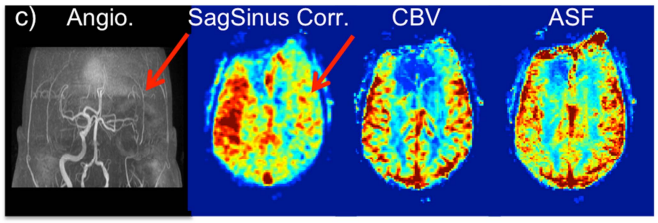


Fig.2 Correlation with major blood vessels







Results: Fig 1b shows a map of signal fluctuations in a volunteer. Contrast between gray and white matter can be observed, and qualitatively, the images appear similar to corresponding CBV map. Highly-vascularised regions also show higher fluctuation values. A high-resolution ASF map in a patient with reperfused stroke and luxury perfusion can be observed in Fig.1c. As indicated by the red arrow, higher BOLD fluctuations are present in the lesion. They correspond to higher CBF and lower Tmax values. Intense bright points can also been observed in the ASF map, which correspond to small regions of haemorrhage. Fig.2b shows vascular correlation maps with the sagittal sinus in a volunteer. As for the ASF map, strong contrast can be observed between GM and WM. The corresponding LAG maps shows values that are close to 0, suggesting that the signals are in phase in healthy brains. Fig.2c shows a correlation map (2 slices averaged) in a patient with chronic carotid occlusion. A clear decrease of the correlation factor can be seen in the affected hemisphere. However both CBV and ASF maps show normal values in both hemispheres, suggesting that the correlation map is more sensitive to the large vessel vascular network.

Conclusion: This study suggests that BOLD signal fluctuations can be used to study perfusion without using contrast agents, much like ASL, but perhaps with different image contrast. As such, it could be used in patients with renal dysfunction, contrast allergy, or for challenge paradigms. Higher resolution maps can be obtained and SNR can be improved by acquiring more temporal points. Furthermore, one can also derive resting state connectivity using the same data. Next steps will include comparison with perfusion values (CBV, CBF, Tmax) to better understand the mechanisms of contrast in these ASF and Vascular Correlation maps, study of the effect of choosing different seed signals in the correlation maps, and the influence of frequency filtering.

References: [1] Baudelet et al, Phys. Med. Biol. 2004. [2] Liu et al., JMRI 2007. [3] Wang et al, JMRI, 2008. [4] Schmiedeskamp et al, MRM, 2012. [5] Straka et al., JMRI 2010. **Acknowledgements** Supported in part by the National Institute of Health (NIH 1R01NS066506, NIH 2RO1NS047607, NCRR 5P41RR09784).