Imaging the 'Dis-Connectome': Using Resting-State fMRI to Study Perfusion and Connectivity Deficits in Patients with Cerebrovascular Disease

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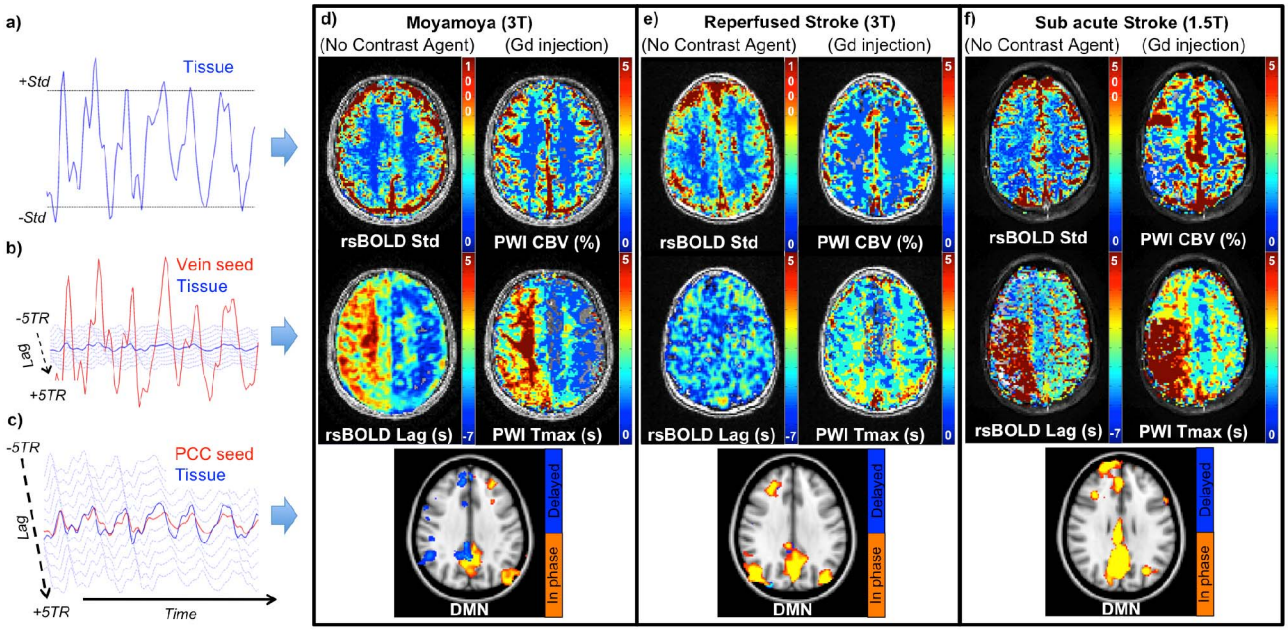
Introduction: Spontaneous fluctuations of the MR BOLD signal are usually acquired to explore the brain's functional organization through the resting-state BOLD (rsBOLD) fMRI analysis. Yet, a few recent reports have suggested that rsBOLD could also be used for perfusion measurements. Amplitude of BOLD fluctuations could be related to blood volume/flow/oxygenation [1-2], while delays in the BOLD signal might reflect arterial arrival time [3]. In this work, we compared perfusion maps obtained with rsBOLD (no contrast agent used) to perfusion maps obtained with Dynamic Susceptibility Contrast (Gadolinium contrast agent) in 20 patients with cerebrovascular diseases. We also derived connectivity maps from the same data and analyzed the influence of time shifting on the results.

Materials and Methods: The local IRB committee approved all studies. 10 patients with newly diagnosed Moyamoya disease (5 women; mean age 42 yrs; range 26-71 yrs) and 10 sub-acute stroke patients (4 women, mean age 53 yrs; range 54-87 yrs) were scanned at 1.5T or 3T (GE Healthcare Systems, Waukesha, WI) with an 8-channel head coil. A gradient echo EPI sequence (TE=30-40ms, TR=1800-2600ms, 20 slices, FOV=20x20 cm, ST=6mm, 128x128) with 120-180 repetitions was used for resting state acquisitions. A gradient echo EPI [4] sequence (TR/TE 1800/34ms, flip angle 90°, 15 slices, 5mm thickness) was used to acquire DSC maps during injection of gadobenate dimeglumine (Gd-BOPTA, Bracco, Milan, Italy). 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). The first ten time points were discarded to avoid transient signal changes before magnetization reached steady state. Then, 3 post-processing methods were used:

- ***rsBOLD Standard deviation****:* The time series of resting-state data were transformed to the frequency domain with a fast Fourier transform, and the amplitude of signal fluctuations was computed as the squared root of the average of the power spectral density for each voxel (Fig1a).
- ***rsBOLD time lag:*** A region of interest was manually delineated over the superior sagittal sinus vein. 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 rsBOLD lag maps were created by taking the maximum of the correlation coefficient over the time lag (Fig1b).
- ***rsBOLD connectivity with lags:*** Default Mode Network (DMN) was probed using a standard seed-based functional connectivity analysis [6]. The ROI of reference was defined as a ~10 mm-radius sphere centered in the precuneus/PCC in the MNI space. The reference time course was correlated against all brain voxels to obtain the 'In phase' functional connectivity map. Delayed reference time courses (+/-5TR) were also used to derive 'delayed' functional connectivity maps (Fig1c).



Results: In all Moyamoya patients, rsBOLD_Lag detected prolonged Tmax values in the affected hemispheres. While overall, there was good correlation between the two approaches (R^2=0.8, large regions of interest), a few differences may be observed on a voxel by voxel basis (see Fig1d). rsBOLD_Std maps showed contrast between gray and white matter, and qualitatively, the images appeared similar to corresponding CBV map. The correlation coefficient was however relatively low (R^2=0.6), possibly reflecting the presence of artefacts at the edges of the brain. In Fig1d, the default mode network (in phase) shows nodes of activation in the healthy hemisphere only. Interestingly, accounting for delays in the analysis seems to bring new nodes in the lesion hemisphere. 4 sub acute stroke patients were completely reperfused and presented normal Tmax, CBV and corresponding normal rsBOLD_Lag and Std. DMN network is complete in Fig1e. In 4 stroke patients, rsBOLD was able to detect long arrival time and low blood volume regions (see Fig1f). Yet, accounting for delays in the connectivity analysis did not detect new DMN nodes. In 2 patients, perfusion lesions were not detected with rsBOLD. Large motion artefacts during acquisition might be at the origin of the discrepancy.

Conclusion: This study suggests that BOLD signal fluctuations can be used to study perfusion without using contrast agents. As such, it could be used in patients with renal dysfunction, contrast allergy, or for challenge paradigms. Furthermore, one can also derive resting-state connectivity using the same data. The influence of delays in perfusion may allow the distinction between networks that are truly affected by disease versus those in whom networks are intact but in which individual nodes are "out of sync" with each other due to delayed perfusion. Several technical improvements of the methods can be foreseen (motion correction, frequency analysis using short TR or external sensors, etc.) and should be used to study the origins of the phenomenon.

References: [1] Liu et al., JMRI 2007. [2] Wang et al, JMRI, 2008. [3] Lv et al., Ann Neurol, 2013. [4] Schmiedeskamp et al, MRM, 2012. [5] Straka et al., JMRI 2010. [6] Biswal et al, MRM, 1995. **Acknowledgements:** Supported in part by (NIH 1R01NS066506, NIH 2RO1NS047607, NCRR 5P41RR09784).