Non-Contrast Mapping of Arterial Delay and Functional Connectivity Using Resting-State functional MRI: a Study in Moyamoya Patients

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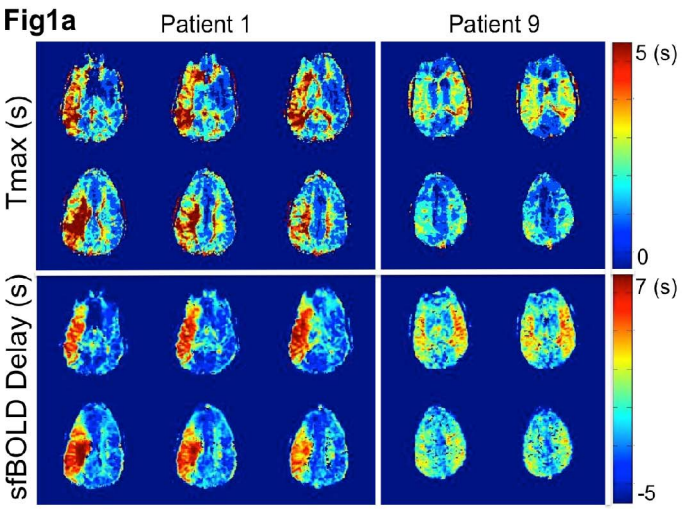
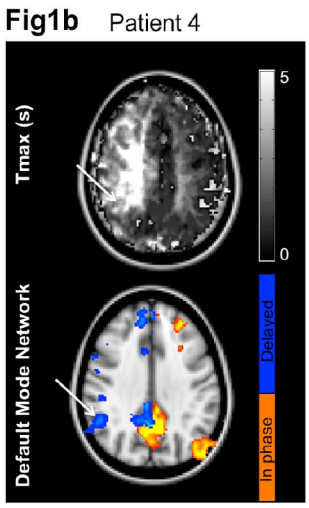
Introduction: While typically used for brain connectivity, temporal relationships between resting-state spontaneous fluctuations of the BOLD (sfBOLD) signal may contain information about arterial arrival delays [1]. In this study, we compared non-contrast sfBOLD delay maps to Tmax maps obtained with gadolinium-based dynamic susceptibility contrast (DSC) in patients with Moyamoya disease, a cerebrovascular disease that is associated with terminal internal carotid artery (ICA) stenosis and occlusion with collateral formation [2]. As such, these patients have Tmax prolongation, primarily in the affected anterior circulation. Two different approaches were used to create the sfBOLD delay maps, using either the whole brain signal or the superior sagittal sinus (SSS) as seed region, and their relationship was investigated. Furthermore, we assessed the effect of arterial arrival delay on rs-fMRI functional connectivity maps.

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) were scanned at 3T (GE Healthcare Systems, Waukesha, WI) with an 8-channel head coil. A gradient echo EPI sequence (TE=40ms, TR=1800ms, 20 slices, FOV=20x20 cm^2, ST=5mm, 128x128) with 120 repetitions (3min36s) was used for resting state acquisitions. The same sequence 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 [3]. 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.

- ***sfBOLD delay maps:*** A region of interest (ROI) was manually placed within the superior sagittal sinus (SSS) in one slice of each patient (approximately 4 voxels). The time evolution averaged over the SSS ROI was recorded as a reference or "seed" time course. Another reference time course was determined from the average signal of the 10 central slices as an approximation of whole brain (WB) signal time course. Cross correlation analysis was then performed between the reference time course and the time courses for all other voxels in the brain. The analysis was performed shifting the time course signal for each voxel between -5TR to +5TR (-9 to +9 s) to determine the offset associated with the highest correlation coefficient with the reference signal. The voxel value for the sfBOLD delay maps was assigned to the offset time that yielded the highest correlation coefficient, provided that the latter was higher than a confidence bound (>95 percent confidence interval). The color scale was inverted to facilitate visual comparison with the Tmax maps.

- ***sfBOLD connectivity with delays:*** Default Mode Network (DMN) was probed using a standard seed-based functional connectivity analysis [4]. 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 (Fig1b).





	Patient	1	2	3	4	5	6	7	8	9	10	Av.	Std
Sag. Sinus	R^2	0.92	0.74	0.88	0.91	0.76	0.95	0.57	0.69	0.59	0.96	**0.80**	**0.15**
	Slope	2.1	0.9	2.27	2.62	1.13	0.75	0.93	0.48	0.51	1.91	**1.36**	**0.79**
	Intercept	-6.7	-3.54	-5.37	-5.88	-2.58	-3.22	-6.55	-3.38	-1.14	-7.88	**-4.62**	**2.15**
Whole Brain	R^2	0.91	0.68	0.67	0.87	0.62	0.57	0.73	0.6	0.29	0.76	**0.67**	**0.17**
	Slope	1.67	0.94	1.1	1.92	0.63	0.41	0.79	0.53	0.15	0.32	**0.85**	**0.58**
	Intercept	-5.45	-2.46	-2.22	-4.38	-1.84	-1.33	-9.39	-1.57	-1.19	-1.73	**-3.16**	**2.59**

Results: There were no regions of reduced diffusion in any of the patients that might correspond to acute infarcts. In all patients, sfBOLD delay maps detected prolonged Tmax values in the affected hemispheres (Fig1a). A stronger linear correlation was found between sfBOLD delays and Tmax using the SSS as reference (r^2=0.8±0.15, slope =1.4±0.8, intercept=-4.6±2.1, 20 large hemispheric ROIs per patient, average±std across patients) compared to WB (r^2=0.7±0.2, slope=0.8±0.6, intercept=-3.2±2.6) (table1). This could be explained by the large amplitude of BOLD fluctuations found in the venous part of the vasculature. A few differences between sfBOLD and DSC maps may still be observed on a voxel by voxel basis (Fig1a). While our acquisition was suboptimal for functional analysis (<4min), most of the DMN network could be detected (orange overlay, in phase, Fig1b). Interestingly, accounting for the delays in the reference signal lead to the identification of new nodes (blue overlay, delayed) in the affected hemisphere (see white arrows in Fig1b).

Conclusion: The findings of this study demonstrate that resting-state sfBOLD imaging can create delay maps similar to Tmax maps without the need for contrast agents in Moyamoya patients. In addition, our results show that accounting for this delay affects the results of functional connectivity maps.

References: [1] Lv et al., Ann Neurol, 2013. [2] Scott RM et al., N. England J. Med., 2009. [3] Straka et al., JMRI, 2010. [4] Biswal et al., MRM, 1995.
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