Perfusion-based functional connectivity mapping of stroke: an arterial spin labeling fcMRI study

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INTRODUCTION: This study is based on the emerging concept of resting state functional networks (RFNs) that depict temporal synchronization of basal neural activity across spatially distributed brain regions. While RFNs have been identified for several functions[1-2] their clinical implications remain unknown. A recent study suggests that RFNs may play a crucial role in stroke recovery[2]. RFNs are ideally suited for studying stroke because the most severe patients can now participate in the study as they are not asked to perform a task but to rest during the entire scanning session. **The primary goal of this study is to assess how perfusion RFNs (pRFNs), identified using ASL fMRI, are affected by hypoperfusion, functional state, and collateral flow in patients with carotid occlusive disease and healthy controls.**
Because of its ease of implementation and optimal SNR, most studies have relied on BOLD fMRI for identifying RFNs. We posit that ASL fMRI is a better option for applications in cerebrovascular disease. Unlike BOLD, ASL provides an absolute measurement of CBF, which makes the comparison with other disease variables more physiologically meaningful. We have developed a tissue-specific ASL (*ts*-ASL) method that is superior to the conventional ASL for mapping long-term alterations in functional connectivity[3].

METHODS: This is an ongoing study where we plan to scan 50 patients and 50 controls. To show the feasibility of ts-ASL for detecting temporal correlations in CBF, we acquired resting CBF and BOLD images from 5 healthy controls (3males, age 64-86 years) and 2 patients with right and left carotid occlusion (>80%), respectively, both females. Neither patient had prior strokes. The patient with right carotid occlusion was asymptomatic (age=82y). The patient with left occlusion suffered form right-hand numbness (age=83y). *Imaging*: MR images are being acquired on a 3.0T Philips Achieva scanner. For each subject we acquire: MPRAGE, resting GE BOLD, FLAIR, and continuous ASL (CASL). With the exception of CASL, all other sequences are routinely acquired in stroke imaging. The temporal resolution is 6s and 2s for ASL and BOLD, respectively. Based on statistical power requirement, the whole-brain time-series for each patient contains 150 points for both BOLD and ASL. Gray matter (GM) flow density maps (CBFd) were obtained using the *ts*-ASL method[3].

FUNCTIONAL CONNECTIVITY (FC) ANALYSIS: 1) *Seed ROI analysis*: The time-series images are entered into a seed-ROI FC analysis. The seed ROIs for Left (L) and Right (R) hemispheres are: motor (M1), Motor Supplemental Area (MSA), Broca's area, and Wernicke's areas. These ROIs were selected based on their relevance for motor and language functions associated with stroke. The time-series for each seed is computed by averaging the signal over all voxels in the seed. (We have found this method is more accurate than averaging around a given Tailarach coordinate.) This process yields 8 average time-series, i.e., 8 coefficient correlational (CC) images per subject for BOLD and ASL, respectively. **2)** *Whole brain Independent Component Analysis (ICA)*: to avoid missing important information beyond our apriori selected ROIs we also employ spatial group ICA and investigate components without ventricular or white-matter contributions that account for a major source of variance in the data (>5%). Correlation matrices are computed and Fisher-Z transformed[4] for each subject for ASL and BOLD, separately.

RESULTS: There was a 20% and 26% hemispheric decrease in CBF in the affected M1 ROI compared to the contralateral M1 ROI for the asymptomatic and symptomatic patient, respectively (p<.005). There was no difference in CBF between left and right M1 ROIs for controls. For controls the CC values were in the [.7-.83] range (well > 0.5 threshold of the study). The graphs for left and right M1 ROIs (Fig.1) show tight correlation of the time series for controls and the asymptomatic patient (both were highly significant, p<.0001); the temporal fluctuations were virtually uncorrelated for the symptomatic patient (p>.2). For controls, we have also acquired BOLD data and found that the average CC was .78 and .71 for *ts*-ASL and BOLD, respectively, boding well with the fact that pRFNs being more robust than bRFNs (Fig.2).

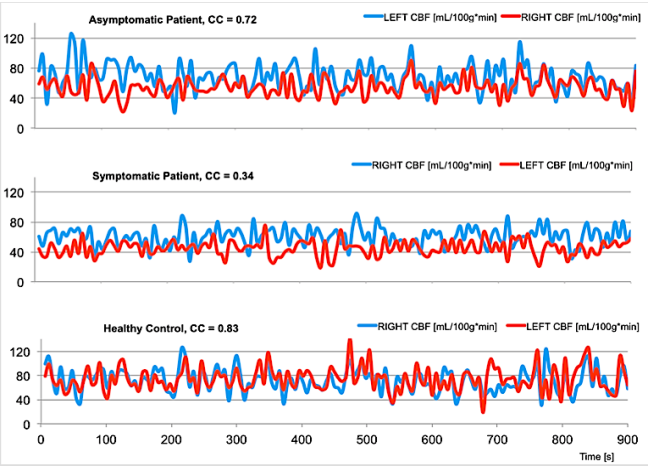

Fig.1: *CBF fluctuation for M1 ROIs from patients and a randomly selected control.* ***NOTE*** *that the correlation coefficient (CC) for the asymptomatic patient was similar to the control's, whereas the fluctuations in the symptomatic patient were essentially uncorrelated.*

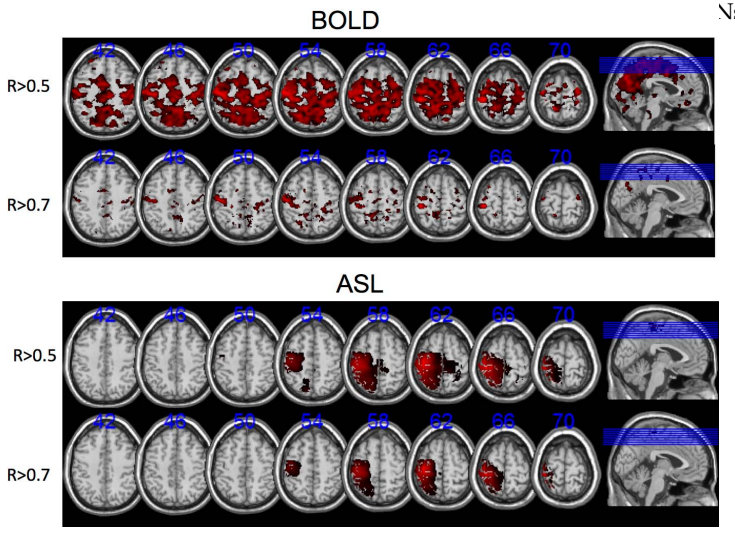

Fig.2: *Comparison of CC maps in motor ROIs for BOLD and ASL in controls. To get a sense of the sensitivity of the connectivity maps, we show them at different statistical thresholds. Note that ASL-based CBF CC maps are more robust than the BOLD maps.*

DISCUSSION: Although these results are very encouraging in that they seem to indicate that CC might be better correlated with expression of symptoms than hypoperfusion, and that ts-ASL may be better suited than BOLD for connectivity analysis, the sample sizes are impermissibly low for any meaningful statistical inference to be drawn. This is an ongoing study and at this stage, we present these data mainly as proof of concept and feasibility analysis.

REFERENCES: [1] Fox et al., *PNAS* 102 (2005); [2] M.Greicius, *CurrOpinNeurol* 21 (2008); [3] Borogovac et al., JCBFM 30 (2010); Calhoun et al., NeuroImage 45 (2009).