Reproducibility of Resting State Functional Connectivity Maps Derived from ASL CBF Data and Concurrent BOLD

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Target audience: Neuroscientists and MRI physicists interested in Functional Connectivity Analysis of the Resting Brain.

Introduction and purpose: In recent years, resting state functional connectivity (rsFC) MRI has become a widely used technique to study networks in the normal brain and their alterations due to pathological conditions (1). Most rsFC studies are carried out using BOLD fMRI (1). Arterial spin labeled (ASL) perfusion fMRI offers the possibility of measuring cerebral blood flow (CBF) and assessing FC by means of evaluating the temporal correlations in the fluctuations of the CBF time series (2). Recent work has shown that ASL rsFC has statistical power comparable to that of BOLD rsFC (3) and could provide a better characterization of low frequency fluctuations than BOLD (4).

The goal of this study was to evaluate and compare the reproducibility of rsFC maps derived from CBF and concurrent BOLD data. To this end, a test-retest study was performed during which ASL perfusion images were acquired using a T_2* weighted sequence, to allow for simultaneous measurement of CBF and BOLD data.

Methods: *Subjects:* 18 healthy subjects (10 females; 24±4 years) participated in the study, after signing a written informed consent.

Scanning protocol: The study was performed on a 3T Siemens Trio using a 12-channel head array. It was carried out in 2 sessions, at least 1 week apart. In each session a resting state perfusion scan was obtained, followed by an anatomical T1-weighed image. The perfusion data was acquired with a pseudo-continuous ASL sequence with a T_2* weighted EPI readout (labeling time = 1.6 s, post-labeling delay = 1.5 s, EPI imaging parameters: TE=20 ms, TR=4 s, resolution=3.4x3.4 mm^2, FOV=220x220 mm^2, 16 slices, slice thickness=6mm, gap=1.5 mm, matrix size=64x64, BW=2365 Hz/pixel). 50 label/control pairs were acquired in a scan time of 6 min.

Data preprocessing and analysis (Matlab scripts, SPM8 and Functional Connectivity Toolbox): Images were realigned and co-registered to the anatomical dataset. CBF images were computed after subtraction of sinc-interpolated label and control images (to minimize BOLD contribution) (5), using the one-compartment model. Concurrent BOLD images were extracted from the label and control series by regressing out a binary covariate representing the effect of labeling. CBF and BOLD images were normalized and smoothed with a 6 mm Gaussian kernel. Seed-to-voxel rsFC analyses were carried out with two seeds: one seed in the left hand motor area (HMA), to assess connectivity within the sensorimotor network, and a second seed in the posterior cingulate/precuneus (PCC), to identify the default mode network (DMN). Left and right HMA masks were manually drawn for every subject on the anatomical images, where the HMA can be identified as an inverted-omega shape in the precentral gyrus. The left HMA seed was defined as a 6-mm-radius sphere centered at the center of gravity of the left HMA mask. The seed in the PCC was a 6-mm-radius sphere centered in [-5, -49, 40] (**Fig. 1**). The realignment parameters and the WM and CSF signals were entered as confounds in the linear regression. The time series were filtered with a band-pass filter of (0.01<f<0.125 Hz) for BOLD data and with a low-pass filter of (f<0.0625 Hz) for CBF data. Seed-to-voxel correlation maps were obtained for each subject. Pearson's correlation coefficients (r) were converted to a normal distribution by Fischer's z transform. Group connectivity maps were obtained for each seed, using one-sample t-tests.

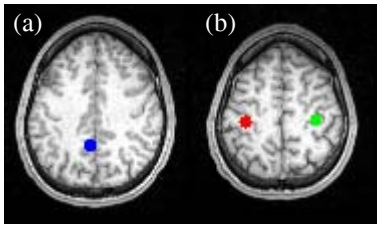

Fig. 1: (a) PCC ROI. (b) Left and right HMA ROIs.

Reproducibility measurements: The test-retest reliability of the correlation strength between HMAs was evaluated by computing the within-subject coefficient of variation (wsCV). For each subject, the correlation strength between left and right HMAs was extracted for each session from the left HMA connectivity maps, and the CV was computed as the ratio of the standard deviation to the mean of the two repeated measurements. The wsCV was then calculated as the squared root of the mean sum of squares of the individual values. The test-retest reliability of the connectivity maps was evaluated by computing the Dice coefficient (DC) and the Root-Mean-Square-Deviation (RMSD), using the two maps obtained per subject, after thresholding (Z > 0.3).

Results and Discussion: **Fig. 2** shows the group rsFC maps obtained with the seed in left HMA and PCC using CBF and concurrent BOLD data. Both techniques were able to reliably identify areas matching the sensorimotor network and the DMN, in agreement with previous reports (6, 7). The statistical power of the BOLD-derived group maps was higher than the power of the CBF-derived maps, likely due to having twice the number of data points in the BOLD time series. There was a high degree of overlap between group maps obtained in both sessions. The results of reproducibility measurements (**Table 1**) show that FC derived from CBF data offers better reproducibility of the connectivity values (as indicated by the lower wsCV), although slightly lower reproducibility of the spatial localization of the identified networks. Concurrent BOLD differs from conventional BOLD, because TE is not optimal.

Table 1 mean (SD)		Sensorimotor network		DMN	
	wsCV	DC	RMSD	DC	RMSD
ASL rsFC	0.25	0.21 (0.07)	0.18 (0.02)	0.26 (0.07)	0.20 (0.03)
BOLD rsFC	0.34	0.33 (0.06)	0.17 (0.04)	0.51 (0.09)	0.17 (0.04)

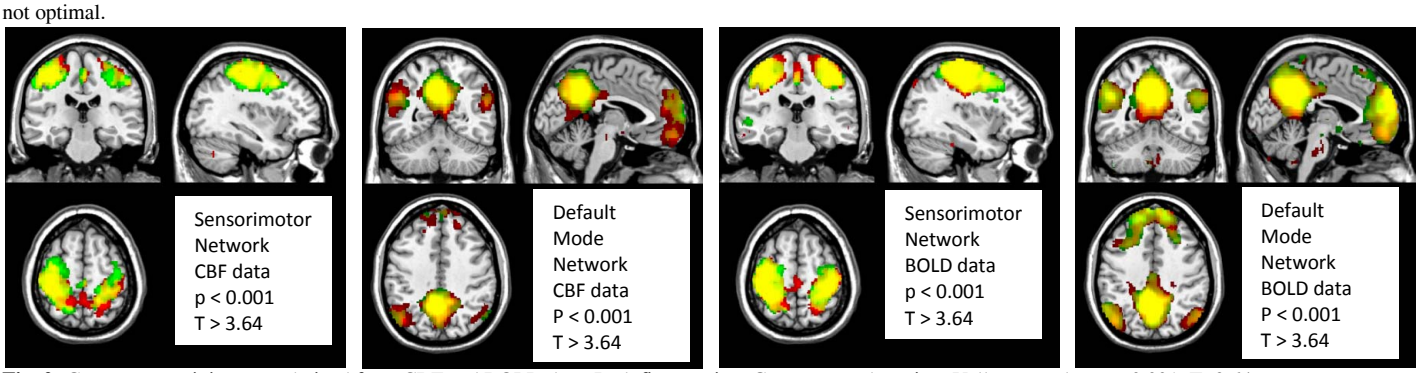

Fig. 2: Group connectivity maps derived from CBF and BOLD data. Red: first session, Green: second session, Yellow: overlap. (p<0.001, T>3.64).

Conclusion: Functional connectivity analysis based on CBF data can reliably identify resting state brain networks, with better reproducibility of the connectivity values than concurrent BOLD, albeit with slightly lower reproducibility of the spatial localization of the identified networks.

References: 1. Auer, Magn Reson Imaging 26:1055-64 (2008). **2**. Biswal et al., NMR in Biomed 10:165-70 (1997). **3.** Vidorreta et al., ISMRM Perfusion Workshop (2012). **4**. Dai et al., ISMRM Perfusion Workshop (2012). **5.** Aguirre et al., Neuroimage 15: 488-500 (2002). **6**. Viviani et al., Plos One 6: e27050 (2011). **7**. Zhu et al., Plos One 8: e65884 (2013). ***Acknowledgements:*** *Grants SAF2011-29344 and RYC-2010-07161.*